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Chem.

SEMINAR TOPICS

Chemistry 135b | II Semester 1938-39

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Madison Hunt, February 8

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R. Mozingo, February 8

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The Synthesis of Chromane Derivatives
H. M. Teeter, February 22

Transformations of the Steroid Group
E. H. Riddle, February 22

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B. R. Baker, March 1

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A. H. Land, March 1

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E. C. Horning, March 8

The Formation of Sulfur-containing Rings
S. C. Kelton, March 8

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R. O. Sauer, March 15

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J. F. Kaplan, March 22

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M. H. Gold, March 29

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L. C. Behr, April 5

Natural Azulenes
J. J. Denton, April 5

Steric Hindrance in Substituted Benzaldehydes
R. V. Lindsey, Jr., April 12

Relation of Basicity and Solubility to the Toxicity of Amines
J. H. McCracken, April 12

The Use of Metallic Complexes in the Determination of Configuration — W. H. Sharkey, April 19

Organic Compounds Containing Selenium and Tellurium — D. E. Burney, April 19

The Chemistry and Structure of Lignin — L. A. Patterson, April 26

Aliphatic Diazo Compounds and Their Reactions with Carbonyl Derivatives — W. H. Rieger, April 26

Some Recent Advances in Chemiluminescence — R. B. Moffett, May 3

Action of Organic Acid Chlorides upon Aliphatic Ethylenic Hydrocarbons in the Presence of Stannic Chloride — H. E. Conde, May 3

Peganine - Vasicine — J. Harkema, May 10

The Tautomerism of _p_-Hydroxyazo Compounds — S. J. Circle, May 17

β-Keto Bases — J. H. Burckhalter, May 17

Isatogens and _iso_-Isatogens — F. C. Dietz, May 24

Mechanism of Ketone Formation from Carboxylic Acids — J. F. McPherson, May 24

Molecular Dissymmetry due to Restricted Rotation in the Benzene Series: An Optically Active Ethylenic Derivative — F. Richter (not reported)

The Formation of Quaternary Ammonium Salts from Dihalogeno-paraffins, etc., in Aqueous Acetone Solution — R. W. Kell (not reported)

γ-Substitution in the Resorcinol Nucleus — J. W. Shackleton (not reported)

Raman Spectra in Organic Chemistry — A. W. Anderson (not reported)

THE PERIODIC ARRANGEMENT OF THE AMINO

ACIDS IN A PROTEIN MOLECULE

Bergmann and Niemann -- The Rockefeller Institute
for Medical Research, New York

The work of Fischer and Hoffmeister has established the peptide bond as the basic linkage between the various amino acids in the protein molecule. No conclusions could be drawn, however, regarding the arrangement of these various amino acid residues in the protein molecule.

Bergmann and his associates have undertaken a careful study of the amino acid content of various proteins with rather striking results. Gelatin was the first protein analyzed by Bergmann. The results of the analysis for glycine, proline, and hydroxyproline are shown in the table below.

Amino acid	Per cent	Molecular Weight	Gram Molecules Found	Gram Molecules Calcd.	Ratio
Glycine	25.5	75	0.34	0.36	6.0
l-Proline	19.7	115	.17	.18	3.0
l-Hydroxyproline	14.4	131	.11	.12	2.0

The data indicates that in a gelatin molecule one-third of the amino acids are glycine, one-sixth are proline, and one-ninth are hydroxyproline. These amino acids can be arranged in periodic order so that every third amino acid is glycine (G), every sixth is proline, every ninth is hydroxyproline; the letter P represents either proline or hydroxyproline in the structures postulated below.

1. -G-P-X-G-X-X-G-P-X-G-X-X-

2. -G-X-P-G-X-X-G-X-P-G-X-X-

Grassmann and Riederle have isolated lysylprolylglycine from the hydrolysis of gelatin. This would tend to support the occurence of a prolylglycine (P-G) unit in gelatin. This unit is found in structure 2 but not in 1.

The data on analysis of egg albumin is shown below.

Amino acid	Per cent	Molecular Weight	Gram Molecules Found	Gram Molecules Calcd.	Ratio	Frequency of Occurrence
Glutamic acid	14	147	0.095	0.101	36	8
Aspartic acid	6.1	133	.045	.045	16	18
Methionine	5.2	149	.034	.033	12	24
Lysine	5.0	146	.034	.033	12	24
Arginine	5.6	174	.032	.033	12	24
Tyrosine	4.2	181	.023	.022	8	36
Histidine	1.5	155	.009	.011	4	72
Cysteine	1.3	121	.010	.011	4	72

Good analytical methods for valine, leucine, and isoleucine are not available; however, good methods for glycine, alanine, proline, hydroxyproline, tryptophane, tyrosine, cystine, methionine, histidine, aspartic acid, glutamic acid and arginine are available.

The average molecular weight of the amino acids formed on hydrolysis of egg albumin is 142; therefore the average weight of an amino acid residue when combined in the protein molecule is 18 less than this, or 124. Thus 100 grams of egg albumin should yield on hydrolysis 0.806 gram molecules of the hypothetical average amino acid. With this value the frequencies of occurrence in the last column were calculated. Since there are four histidine and four cystine molecules per molecule of protein it follows that the minimum number of amino acid residues in a protein molecule is 288. This value multiplied by the average moleeular weight of the residue gives a value of 35,700 for the total molecular weight. This value is in good agreement with that determined by other methods.

A similar calculation from the analysis of blood hemoglobin gave a minimum of 576 amino acid units and a molecular weight of 69,300. This value is also in good agreement with the value obtained by other methods.

From a consideration of the analytical data on a variety of proteins Bergmann concluded that the total number of amino acids in a protein molecule could be represented by the arithmetic expression $2^n x 3^m$ where m and n are small whole numbers. Likewise the number of units of an individual amino acid and its frequency of accurrence in the chain could be represented by the same expression where m and n are either zero or small whole numbers.

Silk fibroin composed largely of glycine and alanine yielded very interesting results when subjected to analysis.

Amino acid	Per cent	Molecular Weight	Gram Molecules Found	Gram Molecules Calcd.	Ratio	Frequency of Occurrence
Glycine	43.8	75	0.584	0.584	1296	2
Alanine	26.4	89	.296	.292	648	4
Tyrosine	13.2	181	.072	.073	162	16
Arginine	0.95	174	.005	.005	12	216
Lysine	0.25	146	.001	.001	4	648
Histidine	0.07	155	.0004	.0004	1	2592

The average molecular weight of the amino acids is 102 which gives 84 for the average weight of the amino acid residue in the protein molecule. Therefore on hydrolysis 100 grams of protein should yield 1.190 gram molecules of the hypothetical average amino acid. Thus the molecular weight is 2592 x 84, or 217,500.

Partial hydrolysis of silk fibroin has yielded glycylalanine (G-A), glycyltyrosine (G-T), alanylglycine (A-G) and alanylglycyltyrosine (A-G-T). It seems unlikely that there are two glycine molecules or two alanine molecules linked together since no alanylalanine or glycylglycine was isolated. Therefore, each glycine unit must be separated from every other glycine unit by one other amino acid. Likewise each alanine unit must be separated from each other

alanine unit by at least three other amino acids. Similar deductions may be drawn regarding the other amino acids present. Hence a partial structure for silk fibroin may be written as follows, where G = glycine, A = alanine, T = tyrosine, Ar= arginine, and X = other amino acids.

G-A-G-T-G-A-G-Ar-G-A-G-X-G-A-G-X-

$($G-A-G-T-G-A-G-X-G-A-G-X-G-A-G-X$)_{12}$

G-A-G-T-G-A-G-X-G-A-G-X-G-A-G-Ar-

$($G-A-G-T-G-A-G-X-G-A-G-X-G-A-G-X-$)_{13}$

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Grassmann and Riederle, Biochem. Z., <u>284</u>, 177 (1936).
Bergmann and Niemann, J. Biol. Chem., <u>118</u>, 301 (1937).
Bergmann and Niemann, J. Biol. Chem., <u>122</u>, 577 (1938).

Reported by Madison Hunt
February 8, 1939

ENZYMATIC SYNTHESIS OF PEPTIDE BONDS

Bergmann -- Rockefeller Institute for Medical Research, New York

The discovery of quantitative rules which govern the biological synthesis of a protein make the process of synthesis of an individual protein molecule appear to be a process involving a high specificity on the part of the enzyme. Not only must the enzyme be capable of synthesizing a peptide bond, but it must also be capable of selecting precisely the structural unit to be used in the process to give the special pattern of the individual protein. The experiments reported here are devoted to a study of this specificity in enzymes which synthesize peptide bonds.

Previous investigators have supposed that under certain conditions hydrolytic enzymes may also function as synthetic enzymes under <u>different</u> conditions of temperature, pH, oxygen tension, etc. These experiments have all been carried out on complex mixtures of protein digestion products. In order to simplify the experimental conditions, the present work has been carried out on very simple substrates. The enzymes which attack proteins act on these substances provided they meet the specificity requirement of the enzyme.

Using the intracellular proteinase, papain, Bergmann and his coworkers were able to show that three different types of reaction occur:

1. Hydrolytic effect. Benzoylglycine amide is hydrolyzed to give hippuric acid and ammonia.

$$C_6H_5CONHCH_2CONH_2 \longrightarrow C_6H_5CONHCH_2COOH + NH_3$$

2. Synthetic effect. Benzoylglycine and aniline yield benzoylglycine anilide.

$$C_6H_5CONHCH_2COOH + C_6H_5NH_2 \longrightarrow C_6H_5CONHCH_2CONHC_6H_5$$

3. Replacement. (a) When benzoylglycine amide is treated with aniline, benzoylglycine anilide is produced.

$$C_6H_5CONHCH_2CONH_2 + C_6H_5NH_2 \longrightarrow C_6H_5CONHCH_2CONHC_6H_5 + NH_3$$

The rate of this reaction is greater than for reaction 1 and can not be a combination of reaction 1 and 2.

(b) Benzoylleucine and glycine anilide react in the presence of papain to give benzoylleucine anilide and glycine.

$$C_6H_5CONH\underset{\displaystyle C_4H_9}{\underset{|}{C}}HCOOH + NH_2CH_2CONHC_6H_5 \longrightarrow C_6H_5CONH\underset{\displaystyle C_4H_9}{\underset{|}{C}}HCONHC_6H_5 + NH_2CH_2COOH$$

All of these reactions occur under identical conditions of pH, etc.

Just which one of these reactions will occur at a given time under a given set of conditions is determined by two factors: the specificity of the enzyme and the substrate present. This may be

illustrated by the following examples (with papain, except 2b).

1. Only the natural form of the amino acid or dipeptide takes part in any of the enzymatic reactions.

2. The arrangement of amino acid residues in the substrate determines the subsequent reactions.

a. Bz-L-G-G ⟶ Bz-L-G + G while

Bz-L-L-G ⟶ Bz-L + L-G

b. (With the enzyme, chromotrypsin)

Bz-T-amide ⟶ no hydrolysis

Bz-T-G ⟶ no hydrolysis

Bz-T-G-amide ⟶ Bz-T + G-amide (quick)

Bz-T-G-G-amide ⟶ slow hydrolysis

c. Bz-L + L-anilide ⟶ Bz-L-L-anilide

Bz-L + G-anilide ⟶ Bz-L-anilide + G

d. Bz-L-L-G ⟶ Bz-L + L-G

Bz-L + L-anilide ⟶ Bz-L-L-anilide

(Bz = benzoyl; L = leucine; G = glycine; T = tyrosine; and A = alanine, or their residues.)

Because of this very complex specificity of proteinases and their ability to act on a variety of substrates a mechanism for protein formation may be advanced. Since on any substrate a given proteinase, in general, produces only one reaction, the process may be considered to be of the following type (where R is rudimentary fibroin molecule at any given stage in synthesis):

R + G ⟶ R-G
R-G + A ⟶ R-G-A
R-G-A + G ⟶ R-G-A-G
R-G-A-G + T ⟶ R-G-A-G-T
R-G-A-G-T + G ⟶ R-G-A-G-T-G
R-G-A-G-T-G + A ⟶ R-G-A-G-T-G-A
R-G-A-G-T-G-A + G ⟶ R-G-A-G-T-G-A-G, etc.

Bergmann's interest in this problem has been to obtain information about the physiological and pathological processes that are dependent upon the formation, the presence, or the transformation of proteins.

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Bergmann, J. Biol. Chem., 119, 707 (1937); 124, 1, 7, 321 (1938).
Bergmann, Chem. Reviews, 22, 423 (1938).

Reported by R. Mozingo
February 8, 1939

[illegible]

[illegible] the [illegible] of the [illegible] or [illegible] in [illegible] of the [illegible] condition.

[illegible] of [illegible]

[illegible]

[illegible]

[illegible] very [illegible] variety of [illegible] only [illegible] reaction, [illegible] following [illegible] where [illegible]

[illegible] products [illegible]

[illegible]

[illegible]

ENOLIZATION AND ACIDITY

Arndt -- University of Istanbul

Compounds containing two or three of the following substituents on a $-CH_2$ or $-CH$ group generally possess the property of forming salts with alkalies:

$COOR$, COR, CHO, SO_2R, SO_2OR, SO_2NR_2, CN, NO_2.

This property will be called the "empirical acidity" and means simply that in such compounds there is a relatively loosely bound hydrogen atom which can be removed by alkali with the formation of a salt anion.

The older researches of Claisen, K. Meyer and others were chiefly on di- and tricarbonyl systems, and led to the conclusion that the acidity of these substances was a property of the enol hydroxyl group since the enol forms were isolable as such and proved to be more acidic than the keto forms. This conclusion, coupled with Thiele's suggestion that the empirical acidity is a consequence of enolization and enolization a consequence of the formation of a conjugated system, led to the formulation of the salts of disulfones and sulfonamides as

```
    O                                O
    ‖                                ‖
  R-S=CH-SO2R          and         R-S=N-R
    |                                |
    OH                               OH           OH
                                                  |
                                                //C-OR
in formal agreement with   R-C=C-C=O    and     CH
                             |   |                \
                             OH  R                 COOR
```

The subject of enolization and acidification has been reexamined by Arndt in the light of modern electronic concepts and with the diagnostic aid of diazomethane as a reagent for the location of acidic hydrogen atoms. The standard $FeCl_3$ and bromine techniques are used also and their applications and limitations are discussed.

The first distinction that must be made is between what is called "acidification effect" and "enolizing tendency". That the two can be distinct is seen by the acid character of compounds which, on the basis of the octet theory, cannot enolize, such as disulfones. Such compounds show no colors with $FeCl_3$, do not absorb bromine but dissolve in aqueous alkali and show C-methylation with diazomethane.

The "enotropic" effect is the tendency for the change

$$CH\text{-}C{=}O \longrightarrow C{=}C\text{-}OH.$$

The work done in transferring the proton from C to O is the "prototropic expenditure of work", and the tendency towards enolization is proportional to the enotropic effect and inversely proportional to the prototropic expenditure of work. The possibility of conjugation increases the enotropic effect, but the acidifying effect is entirely different from the enotropic effect.

In non-enolized combinations (e.g., disulfones) the "empirical acidity" is identical with the $>$CH acidity; in completely enolized

[illegible] AND ACIDITY

Arndt -- University of Istanbul

Compounds containing two or three of the following substituents: [illegible] -SO- or -CN group generally possess the property of [illegible] with alkalies.

[illegible]

This property will be called the "acidity" [illegible] that in such compounds there is a relatively weakly bound [illegible] atom which can be replaced by alkali with the formation of a salt.

The older [illegible] of [illegible], [illegible] and others [illegible] acidity of these substances [illegible] of the [illegible] hydrogen [illegible] since the enol forms were isolated [illegible] than the keto forms. This conclusion, [illegible] that the empirical acidity is a consequence of [illegible] a consequence of the formation of a conjugated system, [illegible] the formation of the salts of [illegible]

[illegible]

is formed together with [illegible]

The subject of [illegible] Arndt in the light of modern [illegible] [illegible] aid of discussion of [illegible] hydrogen atoms. [illegible] and their applications [illegible]

The first distinction [illegible] "electromeric effect" [illegible] is seen by the acid strength [illegible] of the [illegible], ordinary [illegible] mesomeric [illegible] in aqueous alkali and their [illegible]

The "[illegible]" effect is [illegible]

[illegible] ⟵ [illegible]

We note that in translating [illegible] the proton from [illegible] regard [illegible] of [illegible] proportional to the [illegible] effect [illegible] the possibility [illegible] the [illegible] effect, but the [illegible] different from the [illegible] effect.

In non-[illegible] conditions (i.e., [illegible]) the [illegible] acidity is identical with the [illegible] acidity is [illegible]

systems (e.g., β-ketoaldehydes) the "empirical acidity" is identical with the -OH acidity.

Upon these general principles has been based the study of a great variety of compounds, representatives of which are given in the table.

As a result of comparisons between the large number of substances containing various combinations of the groups mentioned, Arndt has arrived at the following series of relative effectiveness:

Acidifying effect:

$$NO_2 > SO_2OR > SO_2R > CN > COOR > CHO > \underset{R}{C}=O$$

Electromeric effect:

$$CHO > \underset{R}{C}=O > CN > COOR > NO_2$$ (groups containing $-SO_2-$ have none)

Certain of the facts adduced in these studies are not incontrovertible For example, the "indirect methylation" of non-enolized compounds to enol ethers needs a more thorough explanation than has been given, for upon this hypothesis rests a large portion of Arndt's conclusions.

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Arndt and Martius, Ann., 499, 228 (1932).
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Arndt and Rose, J. Chem. Soc., 1935, 1.
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Reported by T. A. Geissman
E. F. Rogers

Fenruary 15, 1939

TABLE

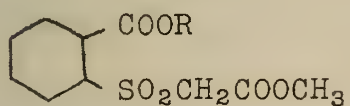
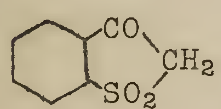
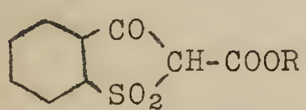
	Compound	Br_2	$FeCl_3$	Type of methylation with CH_2N_2	Remarks
I	$CH_2{<}^{SO_2R}_{SO_2R}$	-	-	no reaction	
II	$CH_2{<}^{SO_2OR}_{SO_2OR}$	-	-	C	Shows $SO_2OR > SO_2R$ in "acidifying effect"
III	$CH_2{<}^{SO_2-CH_2}_{SO_2-CH_2}{>}SO_2$	-	-	C	
IV	Tosyl-CH_2COCH_3	-	-	O	"Indirect" methylation
V	Tosyl-CH_2CHO	-	-	O	
VI		-	-	no reaction	
VII	$^{Tosyl}_{Tosyl}{>}CH-COOCH_3$	-	-	C	
VIII	$^{\phi OSO_2}_{\phi OSO_2}{>}CH-COOCH_3$	-	-	C	
IX	$^{\phi EtNSO_2}_{\phi EtNSO_2}{>}CH-CHO$	+	+	O	Shows $CHO > COCH_3$ in "enotropic effect" (cf. X)
X	$^{\phi EtNSO_2}_{\phi EtNSO_2}{>}CH-COCH_3$	-	-	O	
XI		-	-	O	
XII		+	+	O	(cf. XI) Shows effect of "conjugation partner"
XIII	Tosyl-CH_2CN	-	-	C	
XIV	$CH_2(CN)_2$	-	-	-	
XV	Tosyl-$CH{<}^{CN}_{CN}$	+	+	N	Comp. with TosylCH(COOR shows $CN > COOR$ in "electromeric effect"

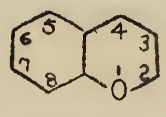
TABLE (cont.)

	Compound	Br_2	$FeCl_3$	Methylation	Remarks
XVI	$CH(CN)_3$	+	+	N	
XVII	Tosyl-CH(COOMe)(CN)	+	+	C,N	Ester C=O not as efficient conjugation partner as CN
XVIII	$CH(CN)_2COOCH_3$	+	+	N	
XIX	Tosyl-CH($COCH_3$)(CN)	+	+	O,C	CO > CN in electromeric effect
XX	RCH_2NO_2	-	-	nitronic ester	
XXI	R-CH=NOOH	+	+	nitronic	
XXII	NO_2CH_2COOEt	-	-	nitronic	
XXIII	$TosylCH_2NO_2$	-	-	nitronic	
XXIV	$\phi COCH_2NO_2$	+	+	$\frac{2}{3}$ nitronic; $\frac{1}{3}$ enol ether	
XXV	NO_2-CH(COOEt)(COOEt)	+	+	nitronic	

THE SYNTHESIS OF CHROMANE DERIVATIVES

John, Günther, and Schmeil -- Göttingen

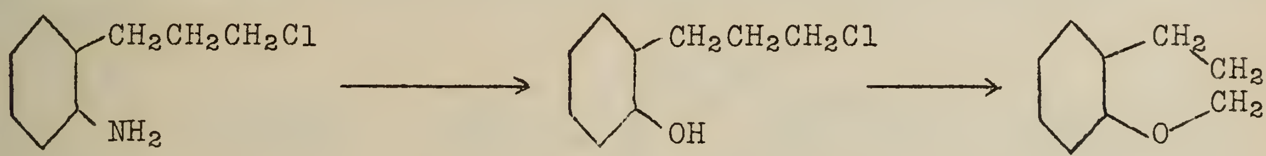
Among the various heterocyclic ring systems which have been investigated, one of great interest and importance is that of chromane. The chromane ring system and its numbering is shown in formula I.



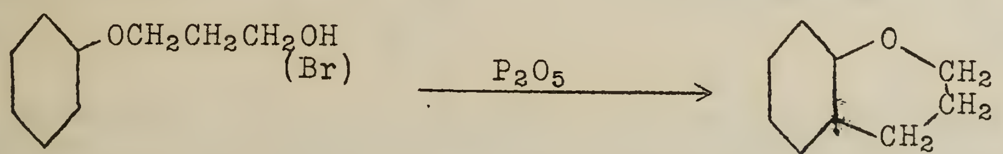
I

Not only have chromane and its derivatives been studied in great detail, but the chromane ring system has been found widely distributed in nature. Some of the natural products containing the chromane ring are -tocopherol, anthocyanidines, flavones, and chatechines. Many chromane derivatives possess physiological properties.

The first preparation of chromane was that of von Braun and Steindorff in 1905. They diazotized γ-chloro-o-propylaniline to introduce an hydroxyl and then brought about ring closure with alkali.

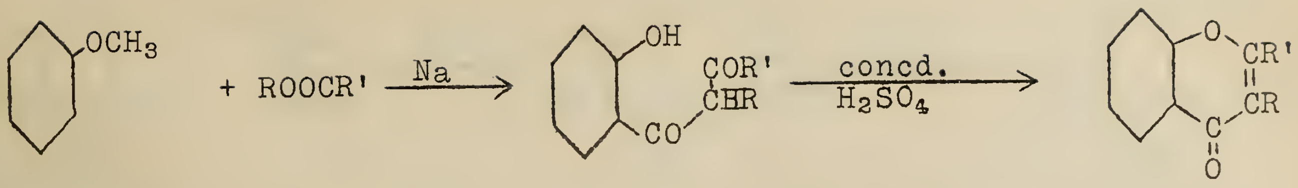


This synthesis is not very useful because of the difficulties in obtaining the starting material and because of poor yields. In 1919-20 the synthesis of chromane was reinvestigated by Rindfusz and coworkers. They succeeded in obtaining two convenient methods of preparation.

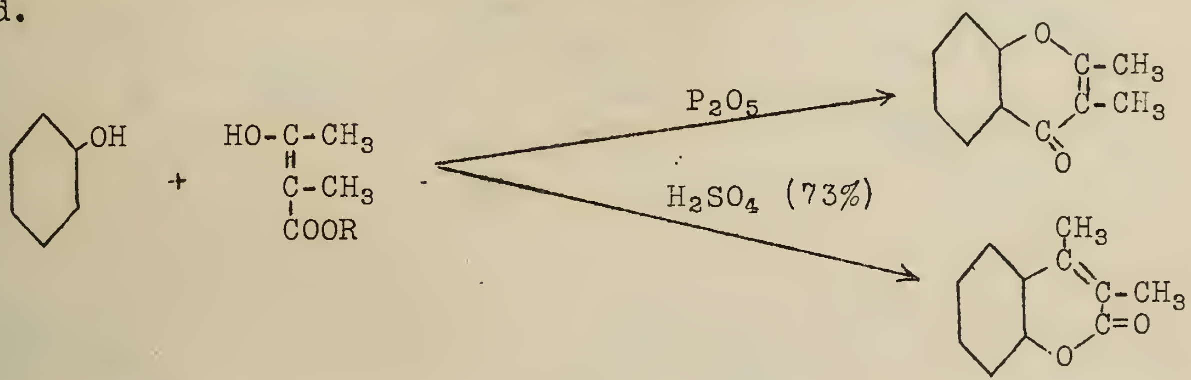


Zinc chloride can also be used as a condensing agent. By the use of substituted phenols, chromane derivatives substituted in the benzene ring are easily obtained. Chromanes substituted in the oxygen ring have been obtained by Claisen by the action of acid condensing agents on mixtures of phenols and butadienes; for example, phenol and isoprene give 2,2-dimethylchromane.

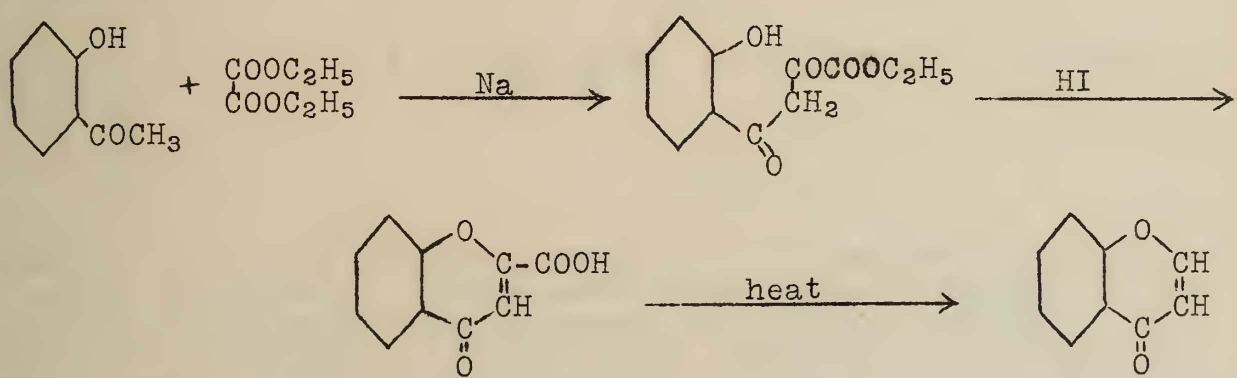
Oxidized derivatives of chromane, namely substituted chromenones have been obtained by two general methods. In the first method o-acetoxyphenyl ethers are treated with esters followed by saponification and ring closure.



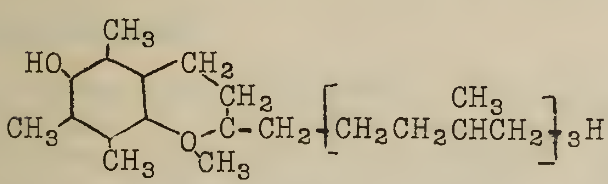
In the second method β-keto esters condensed with phenol. The reaction follows two courses depending upon the condensing agent used.



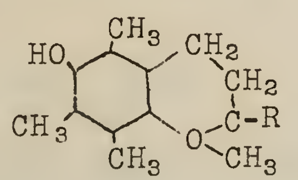
Chromenone 3-carboxylic acid is obtainable from hydroxy-acetophenone and oxalic ester. Upon decarboxylation chromenone itself is obtained.



Demonstration by Karrer that α-tocopherol (Vitamin E) has the structure II, has spurred chemists on to synthesize other chromane derivatives containing the same substituents on the benzene ring.



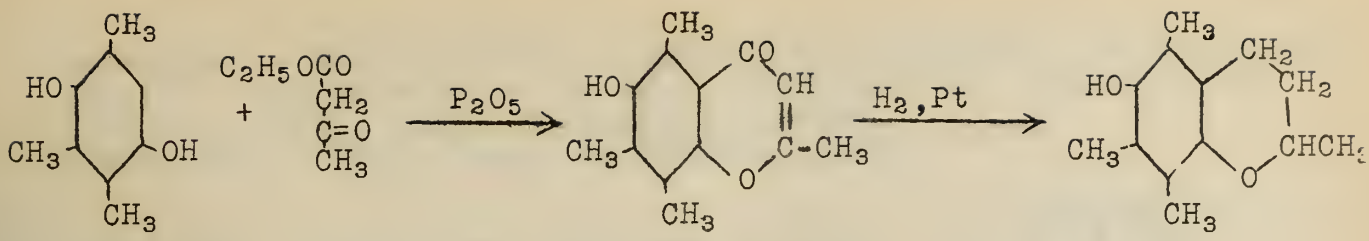
II



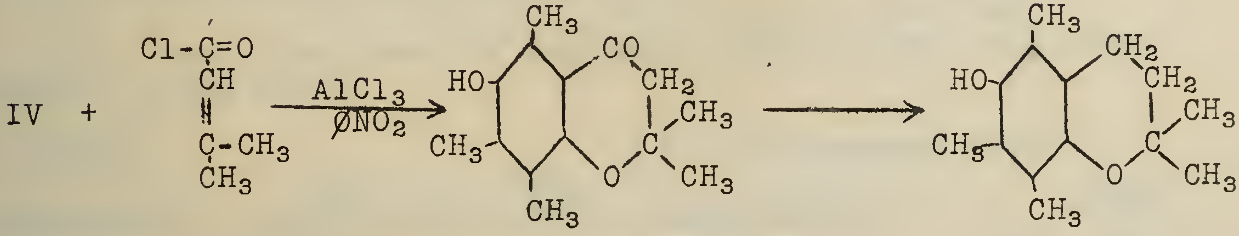
III

$R = H, CH_3, C_{12}H_{25}$

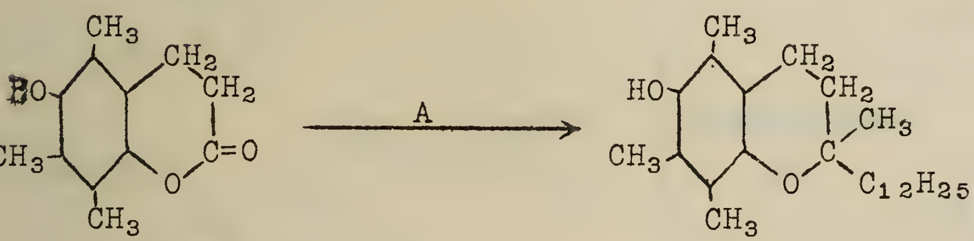
The compounds synthesized have the general structure III. The methods of synthesis used in obtaining these compounds may be classified under three heads: 1. Simonis synthesis; 2. Friedel-Crafts condensation; 3. Grignard reactions. These syntheses are demonstrate by the following examples.



IV V

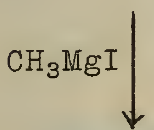


VI



VII

A = 3:4 mixture of CH_3MgI and $C_{12}H_{25}MgI$.



VI

Compounds V, VI, and VII were similar to -tocopherol in that they are easily oxidized to quinones with simultaneous cleavage of the pyran ring and formation of secondary or tertiary alcohols. The ultraviolet absorption spectra of these chromanes are practically identical with that of -tocopherol. Although certain ethers of durohydroquinone and of trimethylhydroquinone show a definite Vitamin E activity, nevertheless compounds V and VI were inactive in doses up to 50 mg. Tests on compound VII have not been completed.

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Rindfusz, Ginnings, and Harnack, ibid., 42, 157 (1920).
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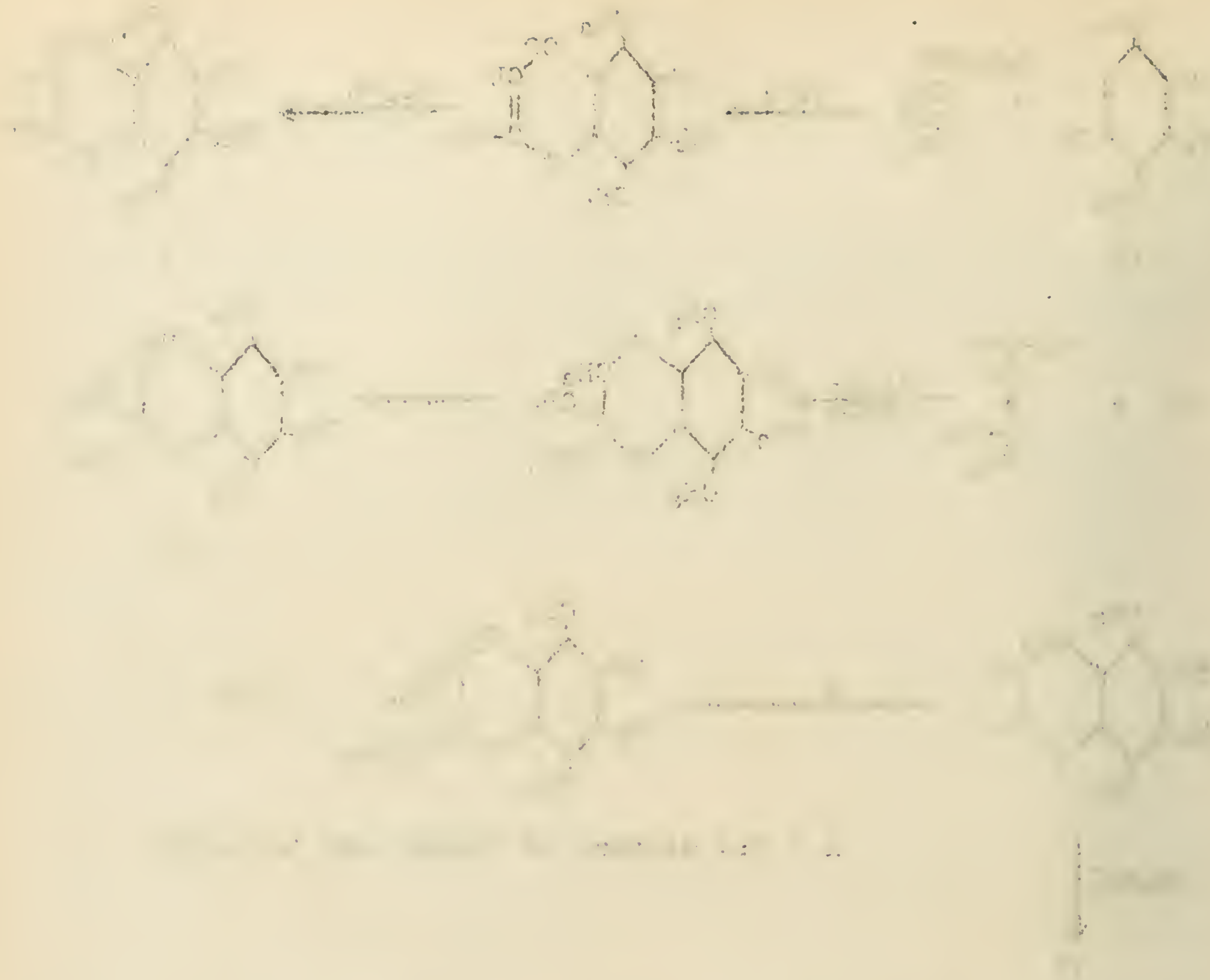
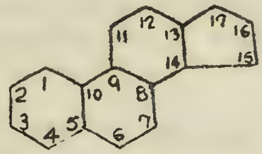
Petschek and Simonis, Ber., 46, 2015 (1913).
Peters and Simonis, ibid., 41, 837 (1908).
John, Gunther and Schmeil, Ber., 71, 2637 (1938).
Smith and Denyes, J. Am. Chem. Soc., 58, 304 (1936).

Reported by H. M. Teeter
February 22, 1939



Butenandt -- Kaiser-Wilhelm Institute für Biochemie, Berlin-Dahlem
Mamoli -- Kaiser-Wilhelm Institute für Biochemie, Berlin-Dahlem
Ruzicka -- Eidg. Techn. Hochschule, Zürich
Reichstein -- Eidg. Techn. Hochschule, Zürich

The name "steroid" was suggested in 1936 by Callow as a convenient designation for the cyclopentanoperhydrophenanthrene group:

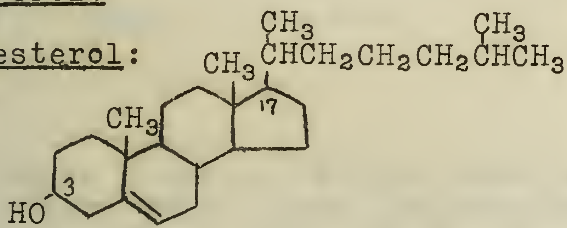


This group includes the following subdivisions, important examples being shown:

A. <u>Sterols</u>

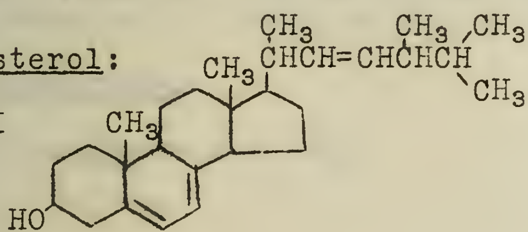
Cholesterol:

I



Ergosterol:

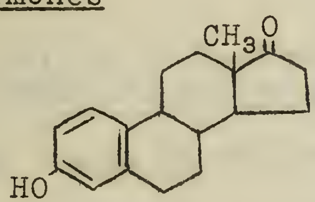
II



B. Sex Hormones

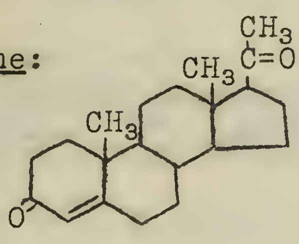
Estrone:

IV



Progesterone:

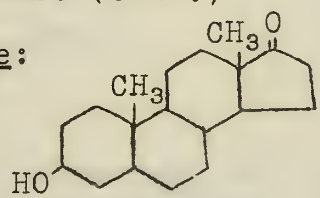
V



B. Sex Hormones (cont.)

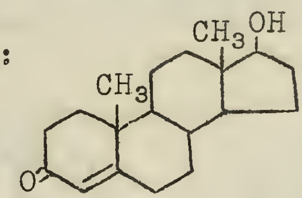
Androsterone:

VI



Testosterone:

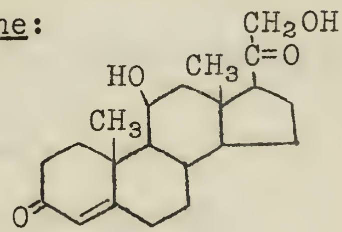
VII



C. Adrenal Cortex Substances

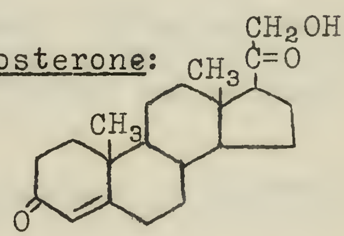
Corticosterone:

VIII



Desoxycorticosterone:

IX



Other members of this group, which will not be treated in this report, are the bile acids, toad poisons, cardiac glycosides, and the digitalis saponins.

The structures of the sterols and bile acids were determined by the usual methods of dehydrogenation and degradation, most of this work occurring in the period 1920-1930. From 1930 to the present, attention has been directed chiefly toward the sex hormones. After preliminary investigations on the small amounts of material available, structures were advanced, and then definitely established by transformations from the known sterols. Transformations from one group to

Butenandt -- Kaiser-Wilhelm Institute für Biochemie, Berlin-Dahlem
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This group includes the following subdivisions, important examples being shown:

A. Sterols

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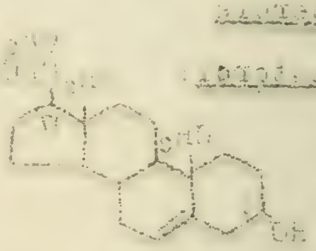
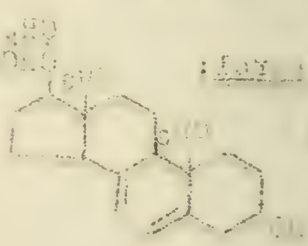
I



Ergosterol:

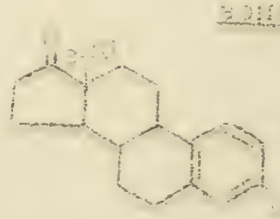
II



B. Sex Hormones

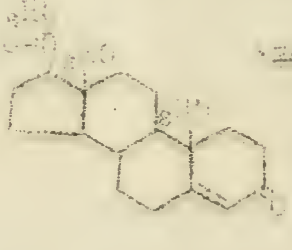
Estrone:

IV



Progesterone:

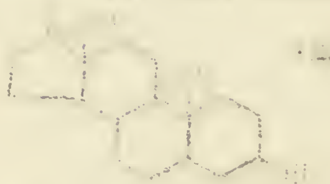
V



B. Sex Hormones (cont.)

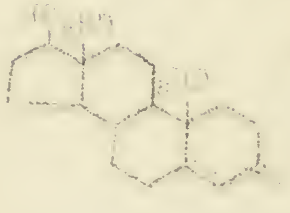
Androsterone:

VI



Testosterone

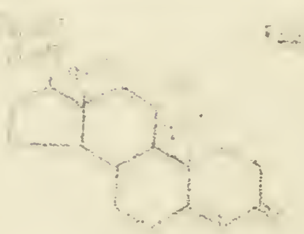
VII



C. Adrenal Cortex Hormones

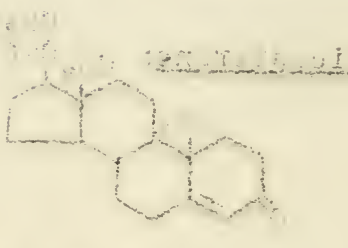
Corticosterone:

VIII



Desoxycorticosterone

IX



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The structures of the sterols and bile acids were established by the usual methods of dehydrogenation and degradation, most of this work occurring in the period 1930-1934. From 1930 to the present, research has been directed chiefly toward the sex hormones. After preliminary investigations on the small amounts of material available, structures were advanced, and then definitely established by transformations from the known sterols. Transformations from one group to

another are thus important for proof of the interrelationship of the groups, and in some cases (particularly for progesterone, V) as preparative methods for less available substances.

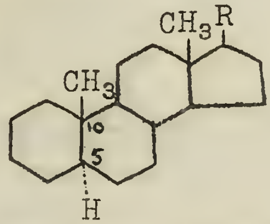
I. <u>Stereochemical Aspects of the Sterols</u> (F-155; G-1251,1377):

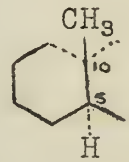
(References to Fieser's "Natural Products Related to Phenanthrene" and to Strain's chapter in Gilman will be designated as F and G, followed by the page number.)

All natural and related products belong to two epimeric ring systems, differing in the configuration of the C_5-H:

1. <u>Cholestane</u>:

C_5-H is <u>trans</u> to C_{10}-CH_3:

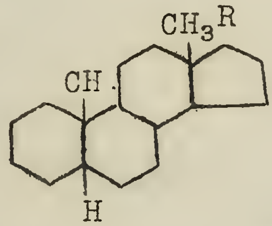


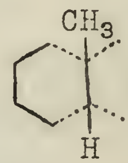


(In these formulas, dotted lines indicate bonds going <u>into</u> the plane of the paper; solid lines indicate bonds coming <u>out</u> of the plane of the paper, referred always to the fused carbons C_5 and C_{10}. See G-1252 for illustration of space models.)

2. <u>Coprostane</u>:

C_5-H is <u>cis</u> to C_{10}-CH_3:





<u>Allo</u> - refers to C_5-H when it is <u>trans</u> to C_{10}-CH_3 (i.e. cholestane might be called <u>allo</u>-coprostane.)

<u>Hydroxyls</u>: (e.g. in cholesterol, I, or androsterone, VI)

<u>Epi</u> - refers to C_3-OH when it is <u>trans</u> to the C_{10}-CH_3.

Configurations are deduced by several methods, the most important being the <u>rule of v. Auwers-Skita</u> (G-1257): <u>neutral</u> media favor formation of <u>trans</u> forms; <u>acid</u> media favor <u>cis</u> (see G-1258 for a chart showing application of this rule).

Marker uses α and β to designate the configuration of hydroxyls:

$$\left.\begin{array}{l}\alpha = \underline{\text{trans}} \\ \beta = \underline{\text{cis}}\end{array}\right\} \text{referred to nearest angular methyl group}$$

II. <u>Transformations of cholesterol (I) to progesterone (V), androsterone (VI), and testosterone (VII)</u>:

The older methods, where they have been replaced by new and bette ones, will not be discussed. In cases where it is difficult, on the basis of the literature, to judge the relative values of the methods, each one is described. A general outline of the steps in the various

[illegible] which are thus important for proof of the [illegible] structure [illegible], and in some cases (particularly for progesterone, V) are [illegible] methods for their available syntheses.

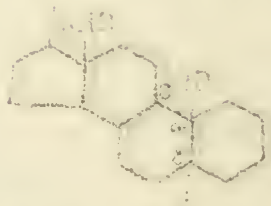
Stereochemical Aspects of the Sterols (F-155; [illegible]-128, 1937):

(References to Fieser's "Natural Products Related to Phenanthrene" and to [illegible] chapter in Gilman will be designated [illegible] by the page number.)

All natural and related products belong to two [illegible] series, differing in the configuration of the C_5-H:

1) [illegible]stane:

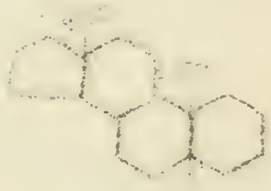
A-B is trans to C_{10}-CH_3.



(In these formulas, dotted lines indicate bonds going into the plane of paper; solid lines indicate bonds coming out [illegible], referring always to the fused carbon [illegible] consideration of space models.)

2) Coprostane.

A-B is cis to C_{10}-CH_3.



allo - refers to C_5-H when it is trans to C_{10}-CH_3 (i.e., cholestane might be called allo-coprostane.)

Epimerism: (e.g. in cholesterol, I, or androsterone, VI)

epi - refers to C_3-OH when it is trans to the C_{10}-CH_3.

Configurations are deduced by several methods, the most important [illegible] rule of V. Auwers-Skita (G-1877): neutral media favor [illegible] formation of trans forms, acid media favor cis [illegible] for a [illegible] application of this rule).

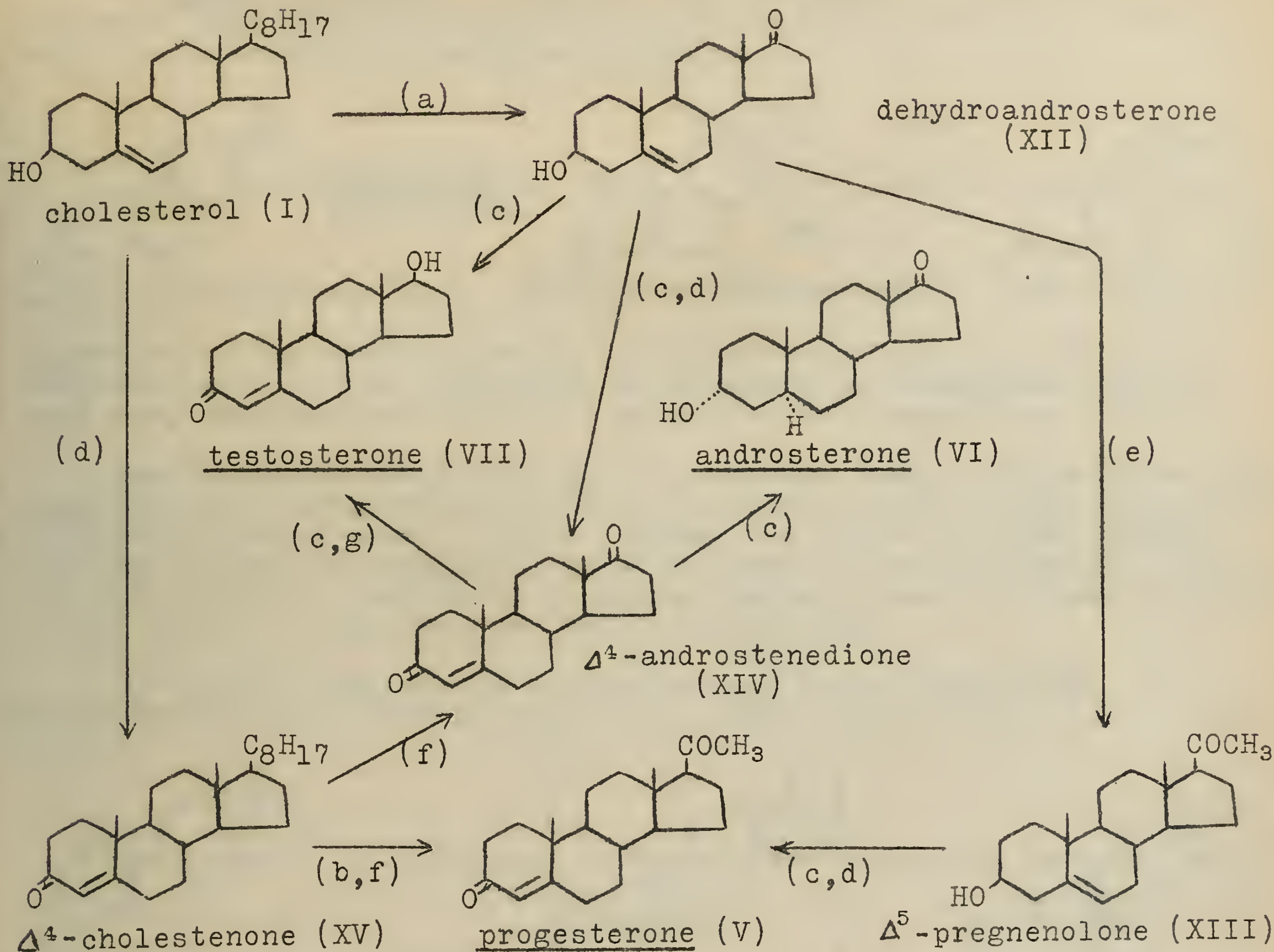
Prefixes α and β to indicate the configuration of hydroxyl:

referring to nearest angular methyl group $\left\{ \begin{array}{l} \alpha = \text{trans} \\ \beta = \text{cis} \end{array} \right.$

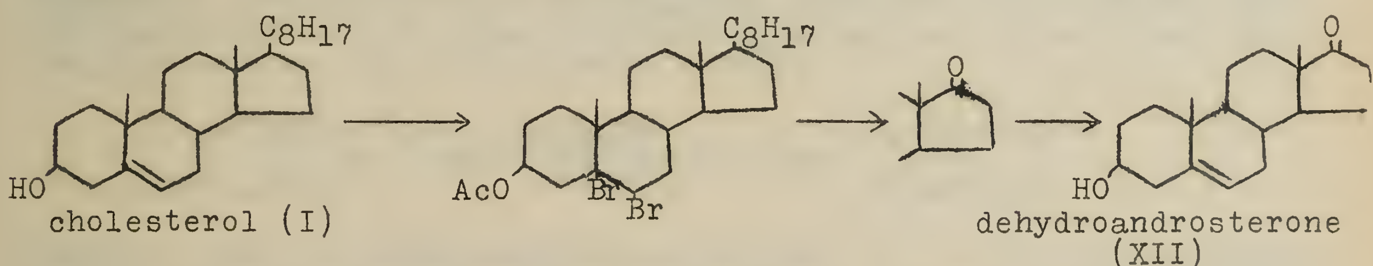
II. Interrelations of the sterol (I) to progesterone (V), androsterone (VI), and testosterone (VII):

The older methods, where they have been superseded by more recent [illegible], will not be discussed. In cases where [illegible] of the literature, to [illegible] the relation [illegible] with [illegible].

conversions is given first, the letters referring to the descriptions of the methods below.

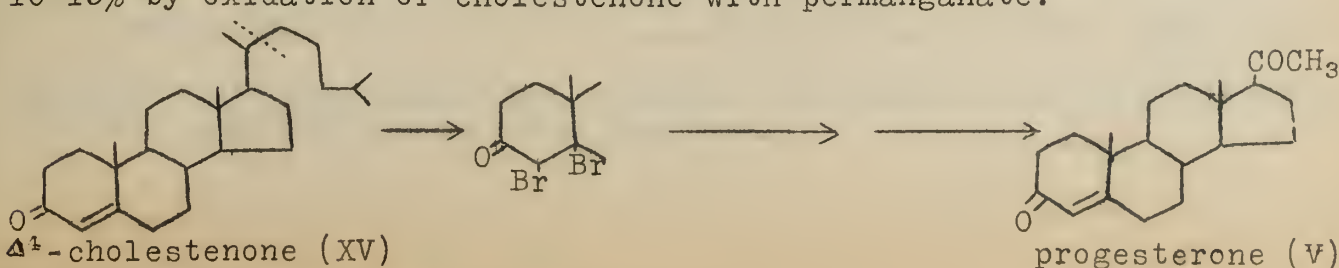


a. Dehydroandrosterone (F-232; G-1375): This important intermediate is now an industrial product, although the overall yield from cholesterol is only 2.8% (F-234; G-1381):

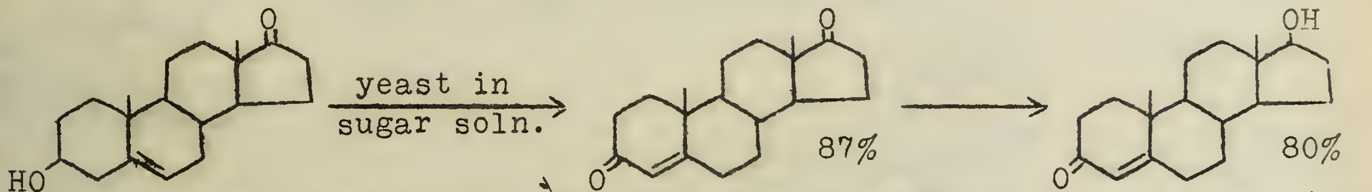


This is the standard method for protecting an ene-ol when oxidizing off the side chain.

b. Tavatsherna (7) has obtained progesterone (V) in yields of 10-15% by oxidation of cholestenone with permanganate:



c. Mamoli's method (3): Mamoli has been able to carry out enzymatic biological hydrogenations and dehydrogenations of steroids with the bacteria in fermenting yeast:

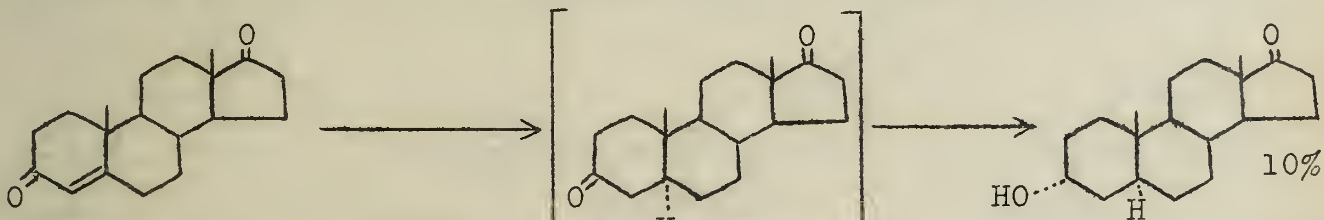


dehydroandrosterone (XII) Δ^4-androstenedione (XIV) testosterone (VII

Migration of the double bond in the first step from C_{5-6} to C_{4-5} is characteristic of the oxidations of Δ^5-ene-3-ol compounds. In the same way, pregnenolone (XIII) is converted to progesterone (V).

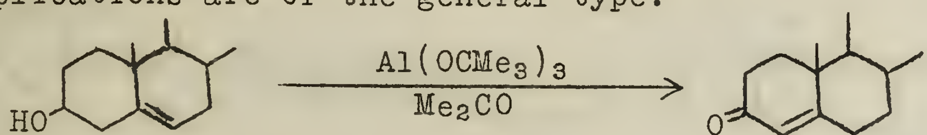
Mamoli has recently been able to convert dehydroandrosterone (XII directly into testosterone (VII) by treatment with a bacterial mixture cultured in yeast water. After shaking for 48 hours under oxygen, the reaction was interrupted, freed of bacteria by filtration, and the filtrate added to completely fermented baker's yeast in sugar solution An 81% yield of testosterone (VII) was obtained.

The latest application of this method is in converting Δ^4-androstenedione (XIV) directly into androsterone (VI):



Δ^4-androstenedione (XIV) androsterone (VI)

d. Oppenauer's method (4): The specific reducing action for C=O of aluminum isopropylate in isopropyl alcohol has been reversed by Oppenauer, and good yields of oxidation products are obtained from secondary alcohols by using aluminum tert-butylate in acetone; all the applications are of the general type:



Examples from the transformations outlined on p. 3 of this abstract:

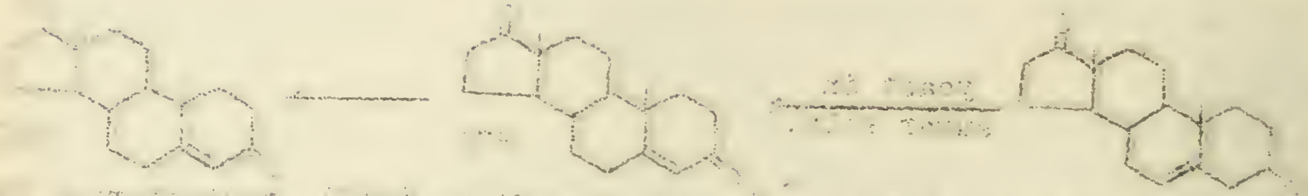
dehydroandrosterone (XII) ⟶ Δ^4-androstenedione (XIV) 85%

Δ^5-pregnenolone (XIII) ⟶ progesterone (V) 75%

cholesterol (I) ⟶ Δ^5-cholestenone (XV) 94%

Westphal (4b) has shown that aluminum isopropylate can be substituted for the tert-butylate in this reaction.

c. *Enzymatic method* (?): Mamoli has been able to carry out enzymatic (biological) hydrogenations and dehydrogenations of steroids with the bacteria in fermenting yeasts:

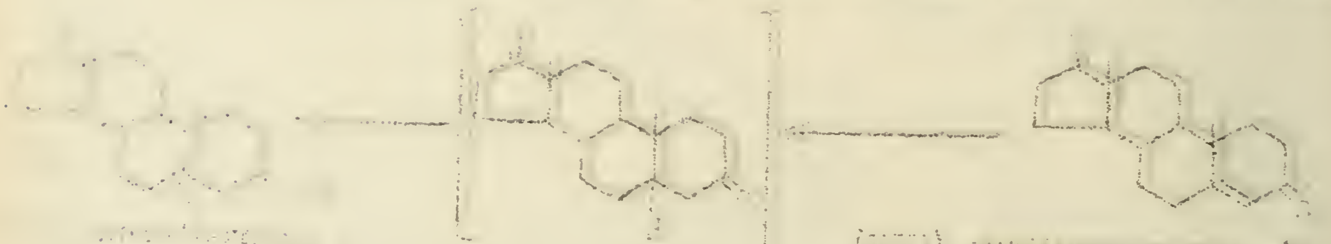


dehydroandrosterone (XXI) Δ^4-androstenedione (XXII)   testosterone (XX)

Hydrogenation of the double bond in the first case [illegible] of the oxidation of Δ^5-3-ol compounds. On the other hand, testosterone (XXII) is converted to androsterone (XX).

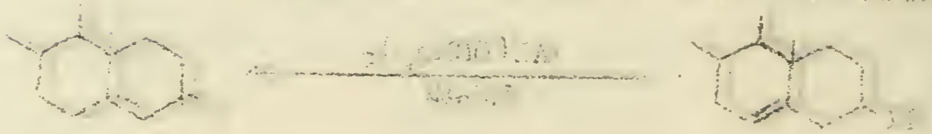
Mamoli has recently been able to convert dehydroandrosterone (XXI) and [illegible] (XXI) by treatment with a bacterium [illegible] in yeast water. After standing [illegible] the oxidation was interrupted, then [illegible] was added to [illegible] fermenting yeast [illegible] of testosterone (XX) was obtained.

The latest application of this method is the [illegible] Δ^4-androstenedione (XXII) directly into testosterone (XX):



Δ^4-androstenedione (XXII)

d. *Oppenauer's Method* (?): The [illegible] according to Oppenauer, [illegible] by aluminium isopropylate in [illegible] acetone, [illegible] and [illegible] of [illegible] are [illegible] by aluminium *tert*-butylate [illegible] the hydrogenation [illegible] of the general type:



Examples from the transformations [illegible] are the following:

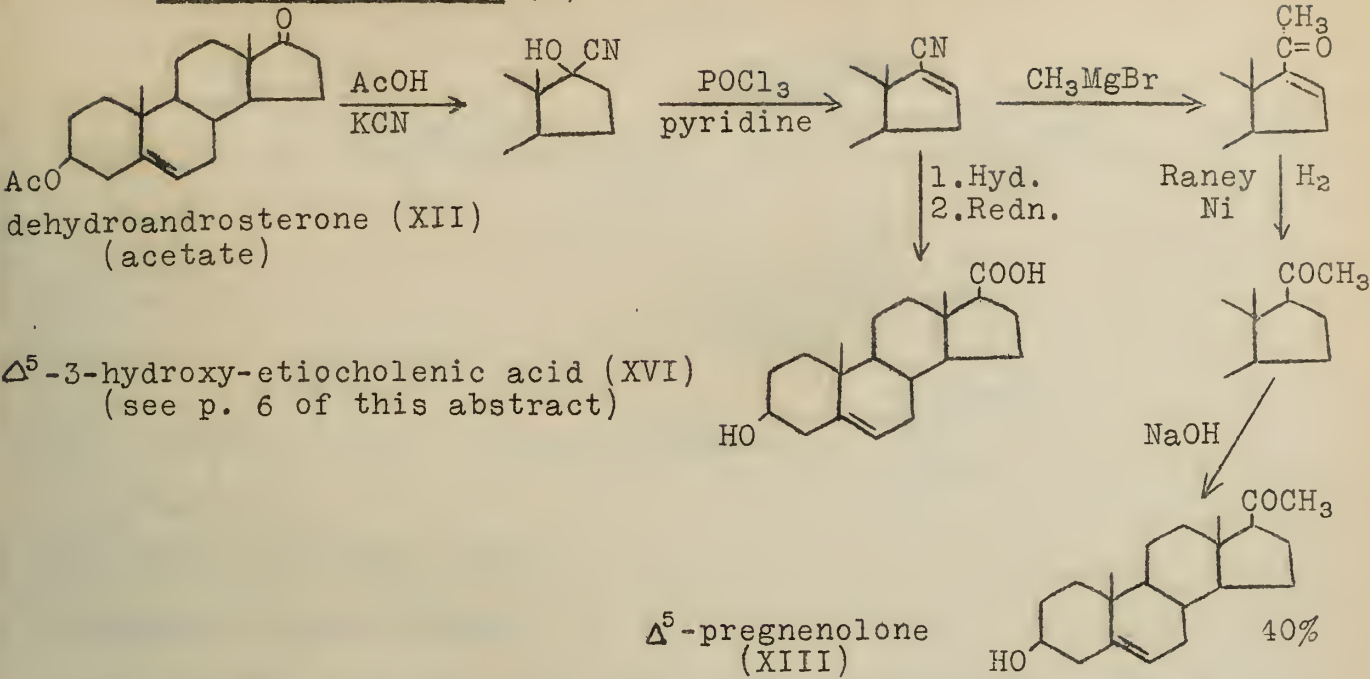
dehydroandrosterone (XXI) ——→ Δ^4-androstenedione (XXII) [illegible]

Δ^5-pregnenolone (XXIV) ——→ progesterone [illegible]

cholesterol (?) ——→ Δ^4-cholestenone [illegible]

Cholesterol (?) has [illegible] by [illegible] from the *tert*-butylate in this reaction.

e. <u>Butenandt's method</u> (5):

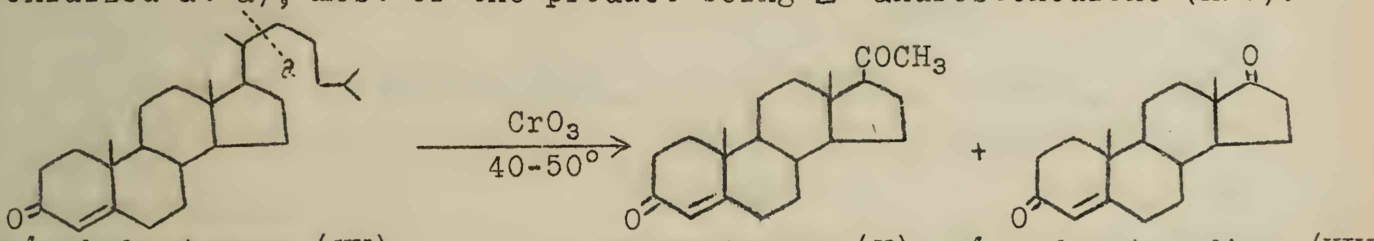


dehydroandrosterone (XII) (acetate)

Δ^5-3-hydroxy-etiocholenic acid (XVI) (see p. 6 of this abstract)

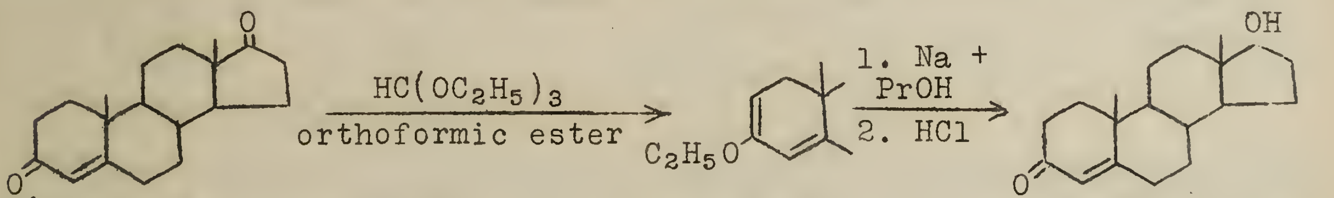
Δ^5-pregnenolone (XIII)

f. <u>Dirscherl</u> (6) has been able to oxidize the side chain of Δ^4-cholestenone (XV) directly with CrO_3, without protecting the C_{4-5} double bond. Progesterone (V) is obtained in small yield (side chain oxidized at a), most of the product being Δ^4-androstenedione (XIV):



Δ^4-cholestenone (XV) progesterone (V) Δ^4-androstenedione (XIV

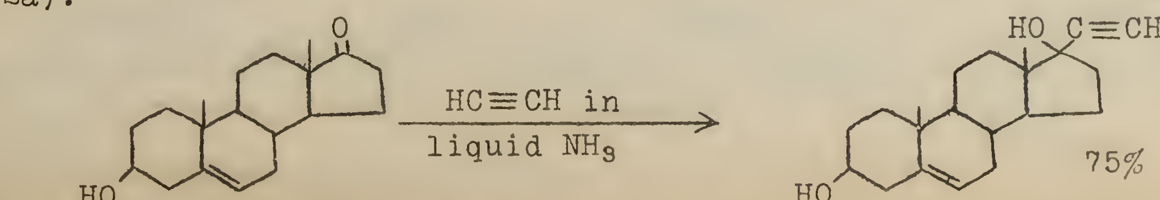
g. <u>Serini</u> (8) has converted Δ^4-androstenedione (XIV) into testosterone (VII) by purely chemical methods (cf. Mamoli's method above):



Δ^4-androstenedione (XIV) enol ether testosterone (VII)

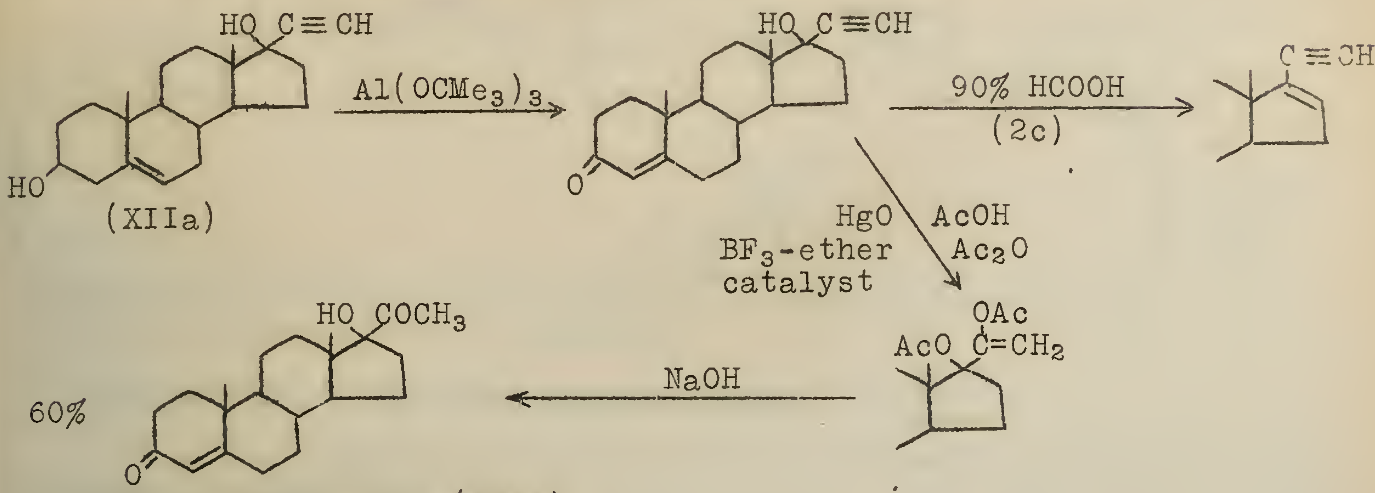
III. <u>Ruzicka's method</u> (2b):

Ruzicka has prepared compounds of the progesterone (V) type by adding acetylene to dehydroandrosterone (XII), followed by acetic acid (2a):



dehydroandrosterone (XII) (XIIa)

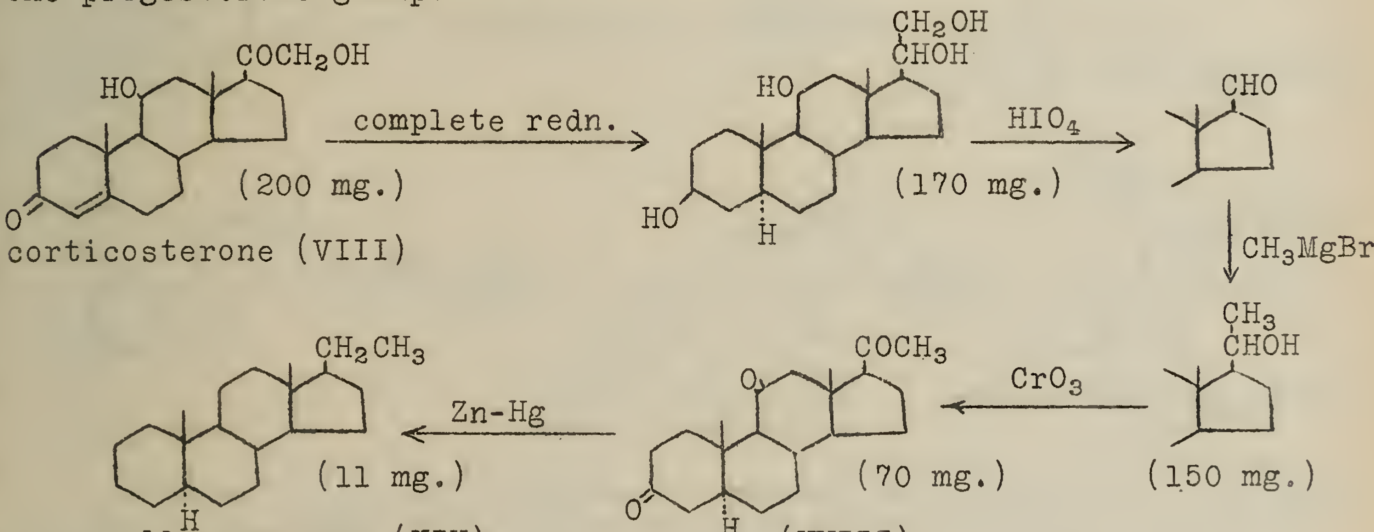
Before adding acetic acid to this hydroxyethynyl compound (XIIa), the C_3-OH is oxidized by Oppenauer's method:



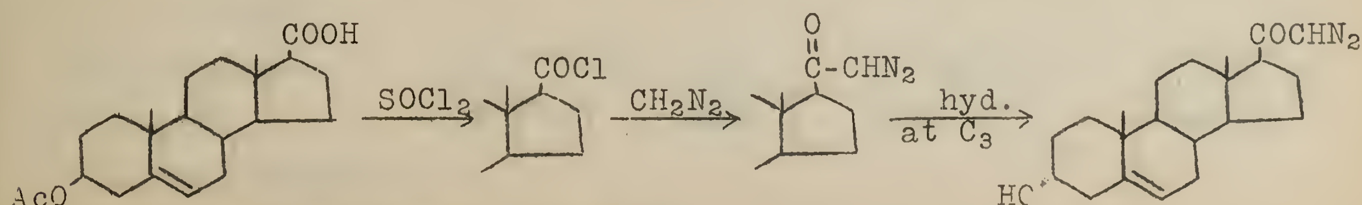
17-hydroxyprogesterone (XVII)

IV. <u>Adrenal Cortex Hormones</u>:

Corticosterone (VIII) has been shown by Reichstein (10a) to be related to the sex hormones by its conversion to <u>allo</u>-pregnane (XIX), the <u>allo</u> isomer (C_5-H <u>trans</u> to C_{10}-CH_3) of the parent hydrocarbon of the pregesterone group:

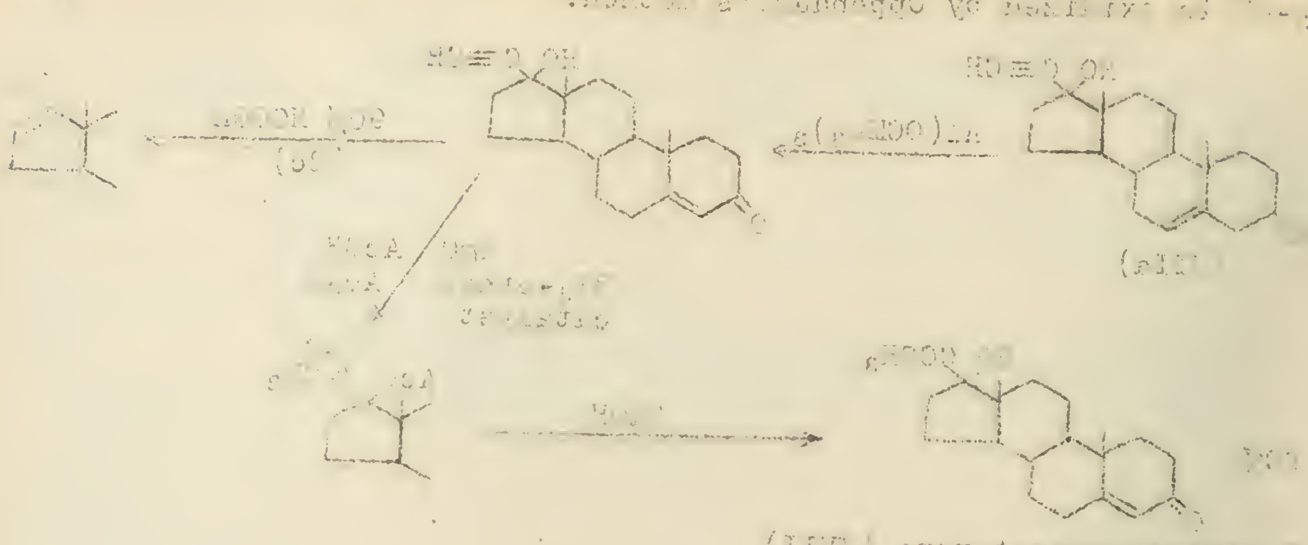


The relation of the adrenal substances to the progesterone group is further shown by the recent isolation (10c) of desoxycorticosterone (21-hydroxy-progesterone, IX) from adrenal cortex, and the discovery that it has 5-7 times greater cortin activity than corticosterone. Reichstein had already synthesized this compound from an etiocholenic acid, using a method of Arndt and Bradley (for references see 10a):



Δ^5-3-hydroxyetiocholenic acid (XVI)
(acetate; see p. 5 of this abstract)

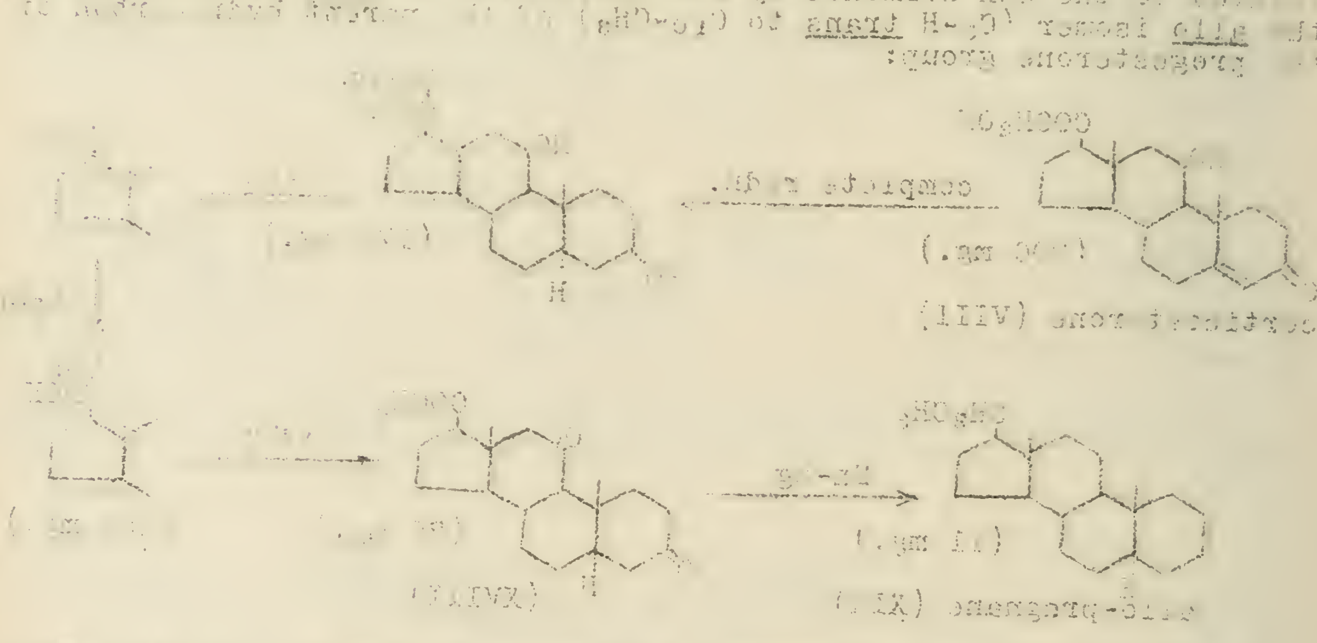
[illegible], adding acetic acid to this hydroxyethynyl compound (VIIa), the [illegible] is oxidized by Oppenauer's method:



17-hydroxyprogesterone (XVII)

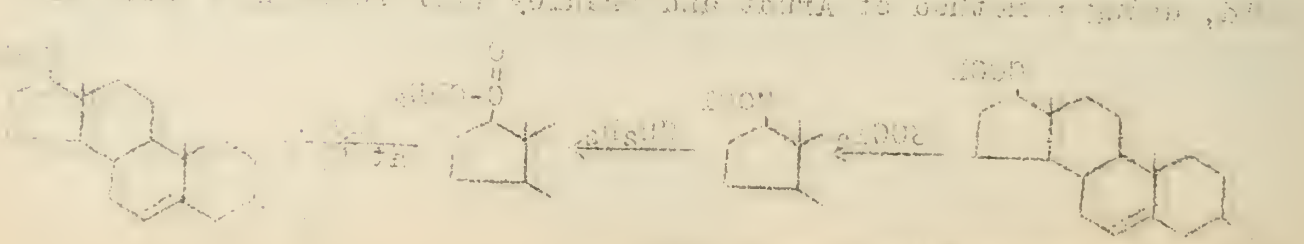
V. Adrenal Cortex Hormones:

Corticosterone (VIII) has been shown by Reichstein [illegible] to be related to the sex hormones by its conversion to allo-pregnane (XIX), the allo isomer (C_5-H trans to C_{10}-CH_3) of the parent hydrocarbon of the progesterone group:

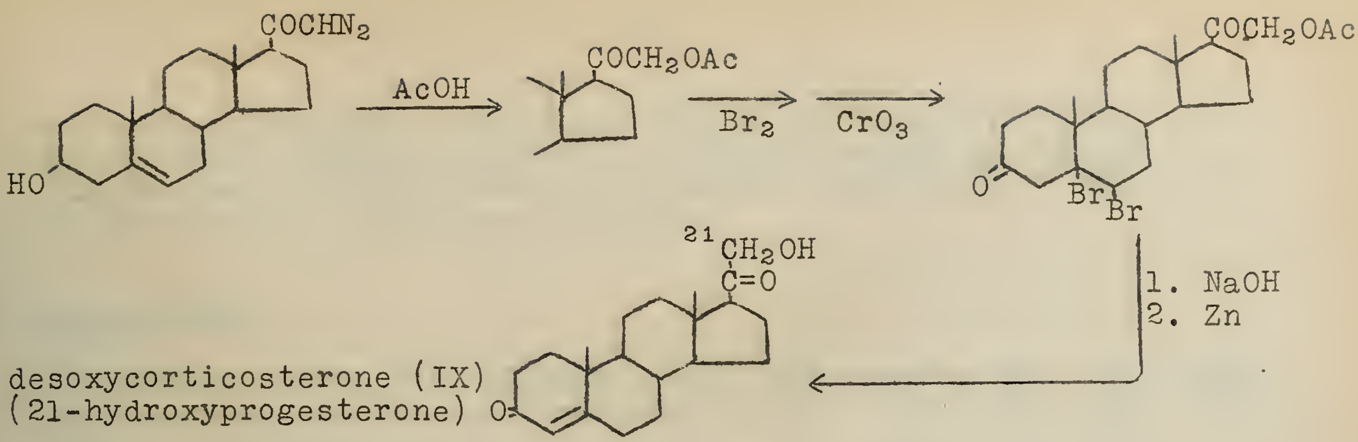


allo-pregnane (XIX)

The relation of the adrenal substances to the [illegible] is further shown by the recent isolation [illegible] of 11-desoxycorticosterone (21-hydroxy-progesterone, XX) from adrenal cortex, and the discovery that it has 5-7 times greater cortin activity than corticosterone. Reichstein had already synthesized this compound [illegible] using the method of Arndt and Eistert [illegible]:

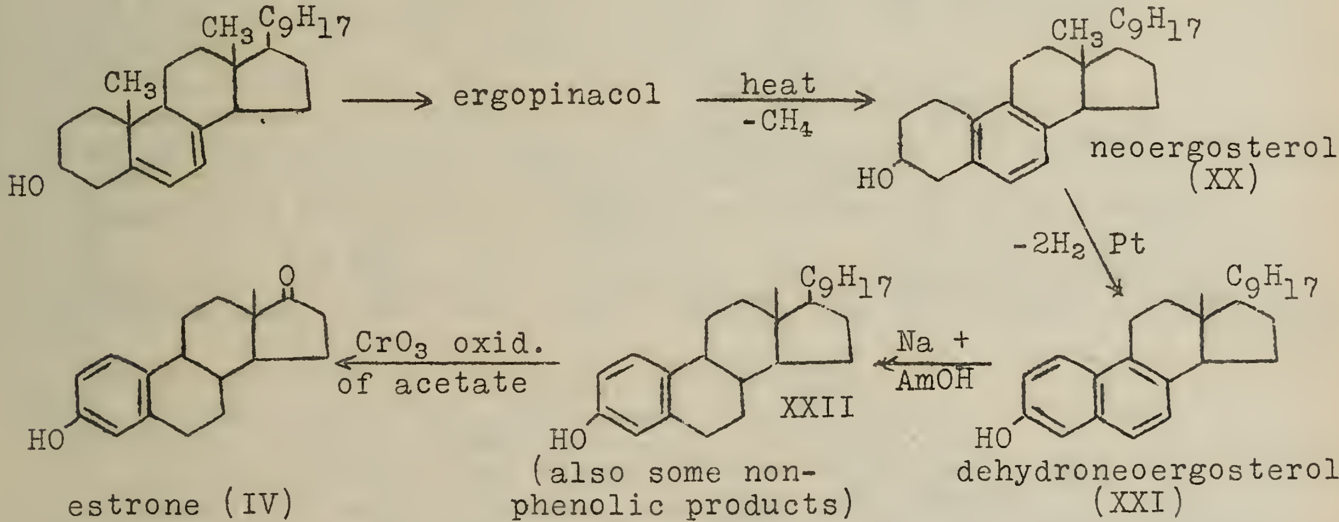


3-hydroxy-etiocholenic acid (XVI)
(see p. 5 of this abstract)

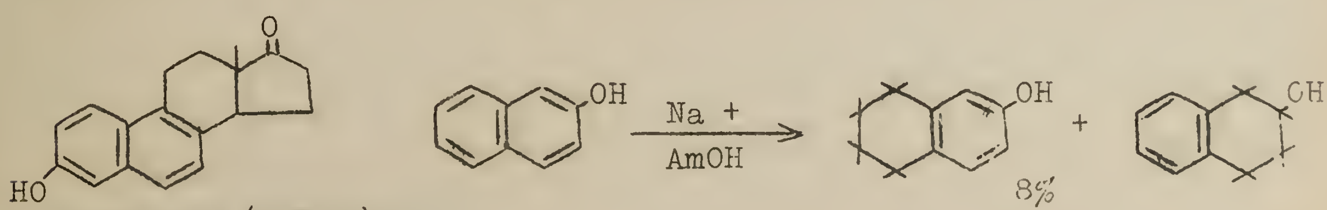


V. Preparation of Estrone from Ergosterol (G-1361):

In 1936, Marker and his associates reported the important conversion of ergosterol (II) to estrone (IV). When ergosterol is exposed to visible light in the absence of O_2, it suffers dehydrogenation and yields a substance of unknown structure called ergopinacol, which by pyrolysis loses the C_{10}-CH_3 as methane, giving neoergosterol (XX) in 30% yield:



Windaus (9a) later attempted to repeat this reduction of dehydroneoergosterol (XXI) with sodium and amyl alcohol to give the phenolic compound XXII, but he obtained no alkali-soluble products, and he questioned the formation of estrone by Marker. The recent article by Marker (9b) on the reduction of equilenin (XXIII) seems to substantiate his earlier work. In support of this, Marker cites the work of Bamberger and Kitschelt (9d) who obtained an 8% yield of ar-tetrahydro-β-naphthol by reduction of β-naphthol with sodium and amyl alcohol.



equilenin (XXIII)

Ruzicka (9c) has also recently studied the reduction of equilenin

with sodium and amyl alcohol and 20% of his reaction mixture contained alkali-soluble (phenolic) products, which he did not characterize. The non-phenolic products, amounting to 80%, were the same as those obtained by Marker.

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Reported by E. H. Riddle
February 22, 1939

with sodium and amyl alcohol and 40% of it [illegible] consisted of alkali-soluble (phenolic) products, which [illegible] characterize. The non-phenolic products, amounting to [illegible], were the same as those obtained by Barker.

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    c. [illegible] and Reichstein, ibid., [illegible] ([illegible]).
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NITRONES

Kröhnke -- Univ. of Berlin

Aromatic nitroso compounds can react with active methylene groups in two different ways to form (1) an azomethine (anil), or (2) a nitrone.

$$C_6H_5CH_2CN + C_6H_5NO \longrightarrow \left[C_6H_5-\overset{CN}{C}H-\underset{OH}{N}-C_6H_5\right]$$

$$1. \quad \left[C_6H_5-\overset{CN}{C}H-\underset{OH}{N}-C_6H_5\right] \longrightarrow C_6H_5-\overset{CN}{C}=N-C_6H_5 + H_2O$$

$$2. \quad \left[C_6H_5-\overset{CN}{C}H-\underset{OH}{N}-C_6H_5\right] + 2\ C_6H_5NO \longrightarrow$$

$$C_6H_5-\overset{CN}{C}=\overset{\overset{O}{\uparrow}}{N}-C_6H_5 + C_6H_5-\overset{\overset{O}{\uparrow}}{N}=N-C_6H_5$$

It is readily seen that an excess of benzyl cyanide will favor reaction 1, whereas an excess of nitrosobenzene will favor the formation of a nitrone 2. In many cases both reactions occur, especially if equal quantities of reactants are used.

If the C-atom of the active methylene contains a halogen, then the reaction proceeds to a nitrone in the presence of alkali with elimination of HX.

$$3. \quad \underline{p}\text{-}NO_2C_6H_4CH_2Cl + C_6H_5NO \longrightarrow \left[\underline{p}\text{-}NO_2C_6H_4CHCl-NOH-R\right] \xrightarrow{NaOH}$$

$$\underline{p}\text{-}NO_2C_6H_4CH=\overset{\overset{O}{\uparrow}}{N}-C_6H_5$$

No excess of nitroso compound is needed as in the second case.

Kröhnke has found that the reaction proceeds more smoothly if the halogen compound is first converted to a cyclammonium salt with pyridine.

$$4. \quad RCH_2X + C_5H_5N \longrightarrow \left[R-CH_2-NC_5H_5\right]^+X^- \xrightarrow{R'NO} \left[RCH\begin{matrix}\diagup NC_5H_5 \\ \diagdown \underset{\diagdown OH}{N}-R'\end{matrix}\right]^+Cl^-$$

$$\xrightarrow{NaOH} \left[RCHOH-NOH-R'\right] \xrightarrow{-H_2O} R-CH=\overset{\overset{O}{\uparrow}}{N}-R'$$

Instead of pyridine other teriary bases as quinoline, isoquinoline or triethylamine can be used. For the nitrosobenzene can be substituted $\underline{p}$-nitrosodimethylaniline. The latter is preferable as dehydration takes place more smoothly.

The aromatic nitrones are well-crystallized stable compounds, while the aliphatic nitrones are not stable and polymerize. The nitrones are more basic than oximes and form stable hydrochlorides.

They are readily hydrolyzed to the corresponding aldehydes or ketones with cold concentrated hydrochloric acid or warm dilute acid. This property offers an excellent method for converting active methylene groups into carbonyls.

$$5.\ C_6H_5COCH_2Br \xrightarrow{C_5H_5N} [C_6H_5COCH_2NC_5H_5]^+Br^- \xrightarrow{(CH_3)_2NC_6H_4NO}$$

$$C_6H_5COCH{=}N{-}C_6H_4N(CH_3)_2 \xrightarrow[\text{acid}]{\text{dil.}} C_6H_5COCHO + (CH_3)_2NC_6H_4NHOH$$

In this case the yield of pyridinium bromide is quantitative. The formation of nitrone goes in 97% yield and the hydrolysis to phenylglyoxal in 90% yield.

The nitrones are also split by such mild reagents as phenylhydrazine, aniline or hydroxylamine. With one mol of phenylhydrazine per mol of benzoyl N-phenylnitrone a mixture of the α and β-phenylhydrazones of phenylglyoxal is obtained. With two moles of phenylhydrazine the osazone is obtained in 76% yield.

With hydroxylamine isonitrosoacetophenone is obtained in 75% yield. With two moles of hydroxylamine a 60% yield of <u>anti</u>-phenylglyoxime is obtained.

With aniline phenylglyoxal dianil hydrate is formed by warming for a few minutes.

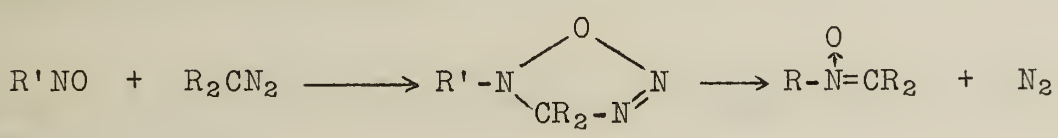
With warm 2N sodium hydroxide the phenylglyoxal obtained from benzoyl N-phenylnitrone is converted directly to mandelic acid in 60% yield.

$$6.\ C_6H_5COCH{=}\overset{\overset{O}{\uparrow}}{N}{-}C_6H_5 \xrightarrow{NaOH} [C_6H_5COCHO] + C_6H_5{-}N{=}\overset{\overset{O}{\uparrow}}{N}{-}C_6H_5$$

$$[C_6H_5COCHO] \xrightarrow{NaOH} C_6H_5CHOHCOOH$$

Nitrones can be prepared in other ways.

A. Staudinger found that diazo compounds react with nitroso compounds to give nitrones.



The nitrones obtained were not as easily isolated pure as by Kröhnke's method.

B. Aldoximes or ketoximes can be alkylated, but not arylated, to give a mixture of the O-ether and the N-ether (nitrone) of the oxime.

$$R_2C{=}NOH + Me_2SO_4 + NaOH \longrightarrow R_2C{=}NOMe$$

$$\longrightarrow R_2C{=}\underset{\underset{O}{\downarrow}}{N}{-}Me$$

C. The condensation of a ketone with a substituted hydroxylamine.

$$R_2C{=}O \; + \; R'NHOH \longrightarrow R_2C{=}\underset{\downarrow \atop O}{N}{-}R'$$

Reactions of nitrones:

1. Hydrolysis to carbonyl compounds.
2. Addition reactions.

According to Smith, all additions take place 1-3 to the system $C{=}N{\rightarrow}O$.

a. With the Grignard reagent

$$C_6H_5CH{=}\underset{\downarrow \atop O}{N}{-}CH_2C_6H_5 \; + \; C_6H_5MgBr \longrightarrow (C_6H_5)_2CH{-}\underset{| \atop OMgX}{N}{-}CH_2C_6H_5 \xrightarrow{H_2O}$$

$$(C_6H_5)_2CH{-}\underset{| \atop OH}{N}{-}CH_2C_6H_5 \quad \text{(N-benzyl-N-benzohydrilhydroxyl-amine)}$$

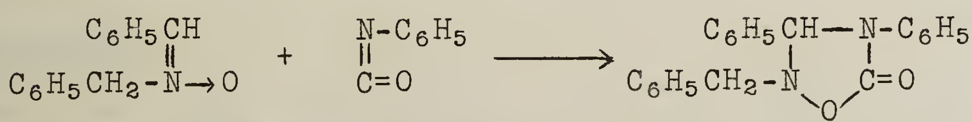
b. With alcoholic potassium cyanide

$$NO_2C_6H_4CH{=}\overset{O \atop \uparrow}{N}{-}C_6H_5 \xrightarrow{KCN} \underset{\text{I}}{NO_2C_6H_4\overset{CN}{\overset{|}{C}}H{-}\overset{OK}{\overset{|}{N}}{-}C_6H_5} \xrightarrow{-KOH}$$

$$\underset{\text{II}}{NO_2C_6H_5{-}\underset{| \atop CN}{C}{=}NC_6H_5} \xrightarrow[C_2H_5OH]{KOH} \underset{\text{III}}{NO_2C_6H_4{-}\underset{| \atop OC_2H_5}{C}{=}NC_6H_5}.$$

I was not isolated, while II can be isolated when equivalent amounts of nitrone and KCN are used. Otherwise the reaction proceeds directly to III in excellent yields.

c. With phenyl isocyanate

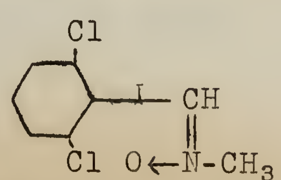


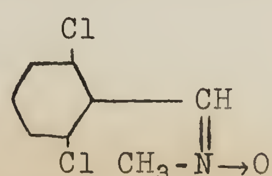
Reactions a and b could be explained by 1-2 addition, but c could hardly be explained in this manner without some form of rearrangement of the addition compound.

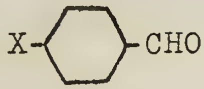
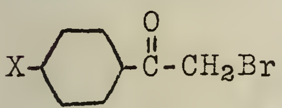
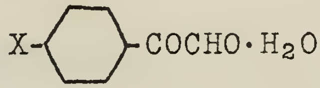
d. Nitrones, in contrast to the O-ethers of oximes, will undergo the Beckmann rearrangement in a <u>trans</u> shift in the same manner as oximes.

$$\begin{array}{c} C_6H_5{-}CH \\ \| \\ O{\leftarrow}N{-}CH_3 \end{array} \longrightarrow \begin{array}{c} C_6H_5{-}C{=}O \\ | \\ H{-}N{-}CH_3 \end{array}$$

Cis-Trans Isomerism: The nitrones should exhibit geometrical isomerism, but only in one case has this been proven with certainty.





Compound	Yield of Pyridinium Salt	Yield of Nitrone	Hydrolysis Product	Yield
	95-99%	52-99%		
X = Br, Cl, NO_2, CH_3O in *o*-, *m*- or *p*- posn.				
	Not given	92-99%		
where X = Br, I, Cl, C_6H_5				75-90%
X-$COCH_2Br$	Not given	60-99%	$XCOCHO \cdot H_2O$	$>$50%
where X = thiophenyl, β-naphthyl, *tert*-butyl				

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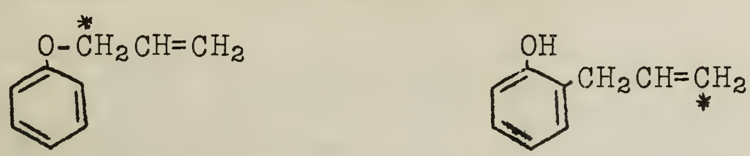
Reported by B. R. Baker
March 1, 1939

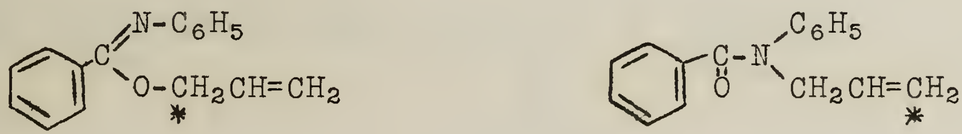
Mumm -- University of Kiel

Phenyl allyl ethers quite readily undergo rearrangement to the corresponding o-allyl phenols in a manner analogous to the rearrangement of enol ethers to $-\underset{\overset{\|}{O}}{C}-CHR$ compounds.

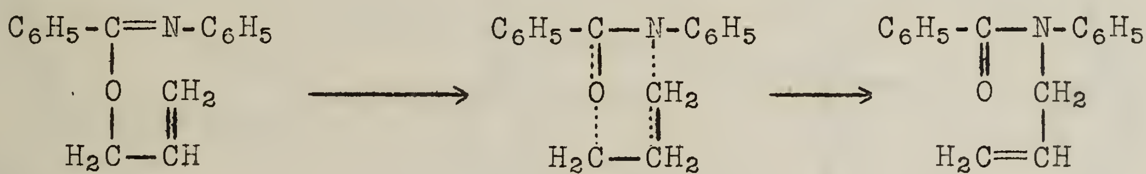
Claisen and Tietze have shown that in some cases at least, the carbon which is bonded to the ring after the rearrangement is not that originally bonded to the oxygen in the ether.



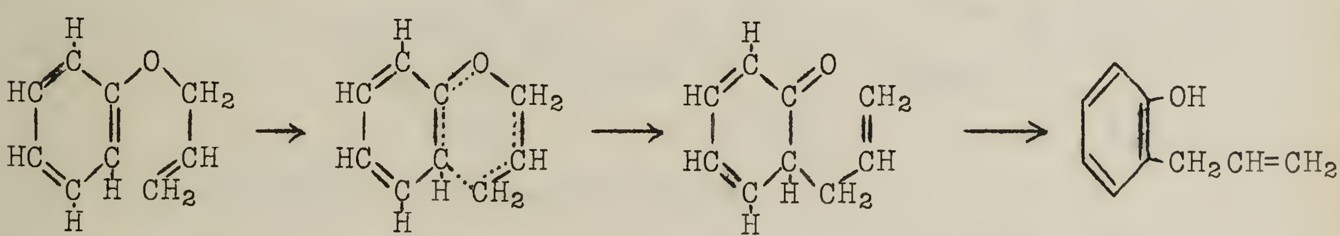
Certain imino allyl esters undergo a similar conversion to N-allyl amides, in the course of which the allyl group exhibits the same shift.



A free radical or an ionic mechanism is untenable in this case since the rearrangement of a mixture of two dissimilarly substituted imino allyl esters yields no product in which an intermolecular interchange of groups has taken place. The formation of an intermediate ring structure by means of single electron bonds is more plausible:



Similarly, for the phenyl allyl ether:



The dotted lines represent single electron bonds, the dashes covalent bonds.

The fact that a shift has taken place is established by use of a substituted allyl group. The reaction follows the same course with either α- or γ-substituted allyl groups.

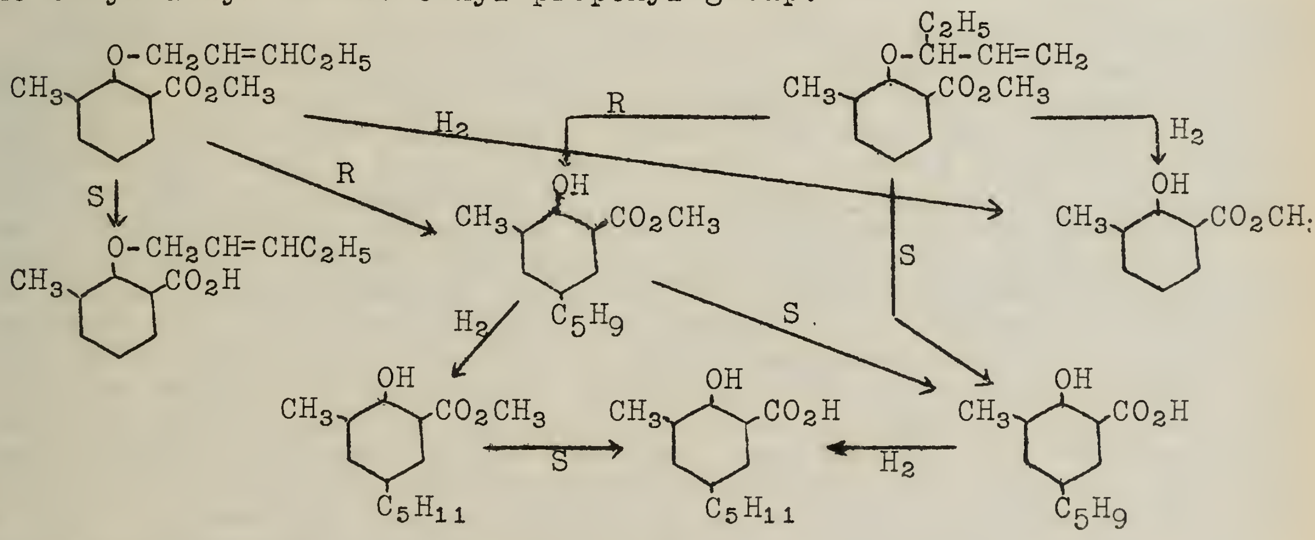
In the case of phenyl allyl ethers substituted in both of the ortho positions the allyl group migrates to the para position. In this case an intermediate ring structure is impossible so the mechanism must involve a splitting into ions or free radicals, and on the basis of other experimental findings, the latter seems more likely. In some examples of this type the migration takes place without involving the α-γ shift. In others, however, the shift does occur. This may be explained on the basis of mesomeric polarization of the migrating free allyl radical. There is evidence to indicate a free radical mechanism may also be involved in the ortho rearrangement in some cases.

The relationships of some of the derivatives of the α- and β-ethyl ethers of methyl o-creosotinate are shown in the chart. It is of interest to note that catalytic hydrogenation of these two ethers results in the cleavage of the ether linkage rather than in the addition of hydrogen to the double bond. One possible inference which may be drawn from this fact is that the addition of the two atoms of hydrogen takes place successively rather than simultaneously. The mechanism of the hydrogenolysis is pictured as follows:

$$C_6H_5\text{-O-}\underset{C_2H_5}{CH}\text{-CH=CH}_2 \xrightarrow{H} C_6H_5\text{-O}^- + \underset{C_2H_5}{C}\text{=CH-CH}_3$$

$$C_6H_5\text{-O}^- \xrightarrow{H} C_6H_5OH$$

The present investigation leaves some doubt as to whether IV contains the ethyl allyl or the ethyl propenyl group.



R = rearrangement; S = saponification.

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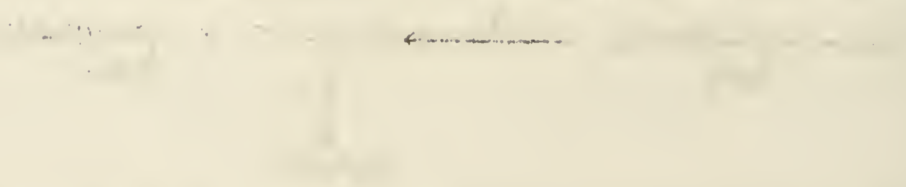
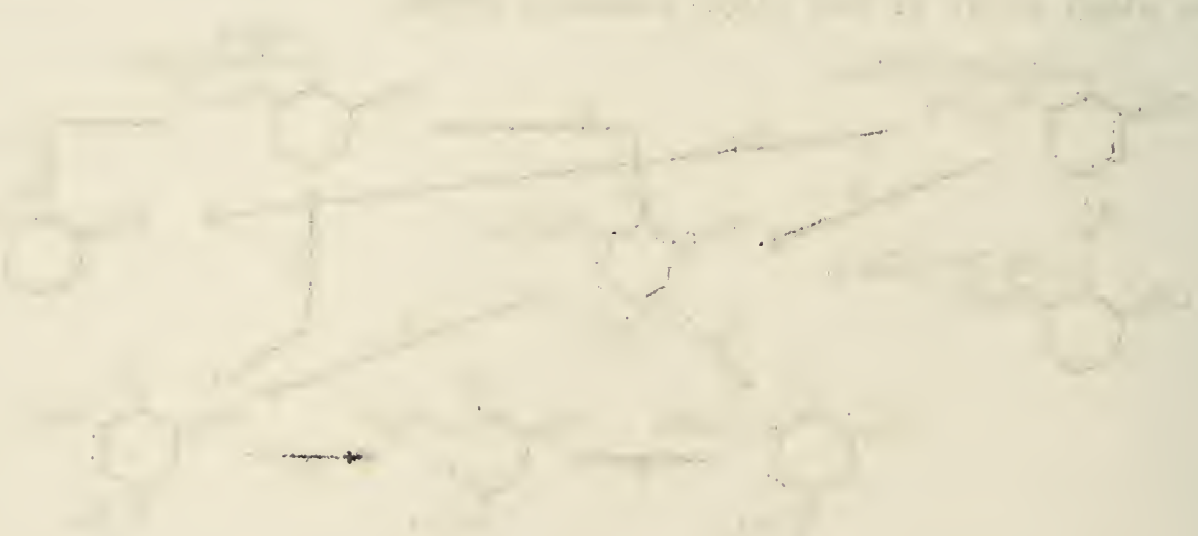
Reported by A. H. Land
March 1, 1939





TOAD POISONS

Munio Kotake -- Osaka

The toad poisons are a group of compounds present in the skin glands of the toad. They have been used for centuries as ingredients of drugs by the Chinese (as Ch'an Su; in Japan as Senso) and in their pharmacological action and chemical structures are closely related to the cardiac poisons obtained from plants. In small amounts a typical emetic action is observed, while larger quantities are fatal. The principal toxin of the toad Bufo bufo bufo will induce systolic cessation of the heartbeat in the cat in doses of 0.3 mg. per kg.

The crude poisons may be extracted from dried toad skins by alcohol, or obtained by expression from the parotid glands of live toads. The toad suffers no injury by this method. Cholesterol, -sitosterol (a plant sterol), adrenaline, a series of tryptamine derivatives, and the poisons proper are present in the crude material. Older methods for the separation of the poisons involved a series of treatments with different common solvents, but later methods have employed these in conjunction with chromatographic absorption. The tryptamine derivatives have been investigated chiefly by Wieland with considerable success. The cardiotonic constituents, which are sterol derivatives, have been studied extensively, but there is some confusion as to the relative identities of a number of compounds isolated by different authors. The best known components, bufotoxin and its derivative bufotalin, were studied by Wieland, and the structure is now known (as of 1936) with the exception of a double bond position. The structure of gamabufogenin has now been determined by Kotake.

Gamabufogenin was first isolated in 1928 by Kotake from 5000 toad skins (B. vulgaris formosus) in 35 g. yield and given the name gamabufotalin. The elementary formula $C_{27}H_{38}O_8$ was determined and a number of derivatives prepared. Among these were the diacetyl and anhydro compounds, and the diformyl ester. Wieland in 1930 isolated gamabufotoxin and gamabufogenin from Japanese toad skins and studied them. Gamabufotoxin was found to be a conjugate of the genin with suberylarginine, and the formulas $C_{38}H_{60}O_{10}N_4$ and $C_{27}H_{35}O_5$ found. The nuclear ring system was taken as the sterol structure, since experiments on other toad poisons indicated this. Chrysene and Diels' hydrocarbon have been isolated in dehydrogenation studies. X-ray data also supports this model. A lactone ring was found, as were two hydroxyls which could be acetylated to give a compound very similar to that obtained by Kotake under the same conditions. The toxin on mild hydrolysis yielded an anhydrogamabufogenin (A) which was not the same as that obtained (B) by the action of strong HCl on gamabufogenin, but could be transformed to the latter by HCl. Hydrolysis of the toxin under stronger conditions gave the compound B directly:

$$\underset{\text{toxin}}{C_{24}H_{35}O_5\text{-}OCOC_{13}H_{25}O_3N_4} \xrightarrow[\text{heat}]{\text{0.5N HCl}} \underset{\text{anhydrogenin A}}{C_{24}H_{32}O_4}$$

$$\underset{\text{anhydrogenin A}}{C_{24}H_{32}O_4} \xrightarrow{\text{conc. HCl}} \underset{\text{anhydrogenin B}}{C_{24}H_{32}O_4}$$

$$\underset{\text{toxin}}{C_{24}H_{35}O_5\text{-}OCOC_{13}H_{25}O_3N_4} \xrightarrow{\text{heat} \quad \text{1N HCl}} \underset{\text{anhydrogenin B}}{C_{24}H_{32}O_4}$$

$$\underset{\text{genin}}{C_{24}H_{34}O_5} \xrightarrow{\text{conc. HCl}} \underset{\text{anhydrogenin B}}{C_{24}H_{32}O_4}$$

[illegible] -- [illegible]

The toad poisons are a group of compounds present in the [illegible] secretions of the toads. They have [illegible] of drugs by the Chinese [illegible] pharmacological action and chemical structure are closely related to the digitalis [illegible] from plants. [illegible] principal [illegible] of the [illegible].

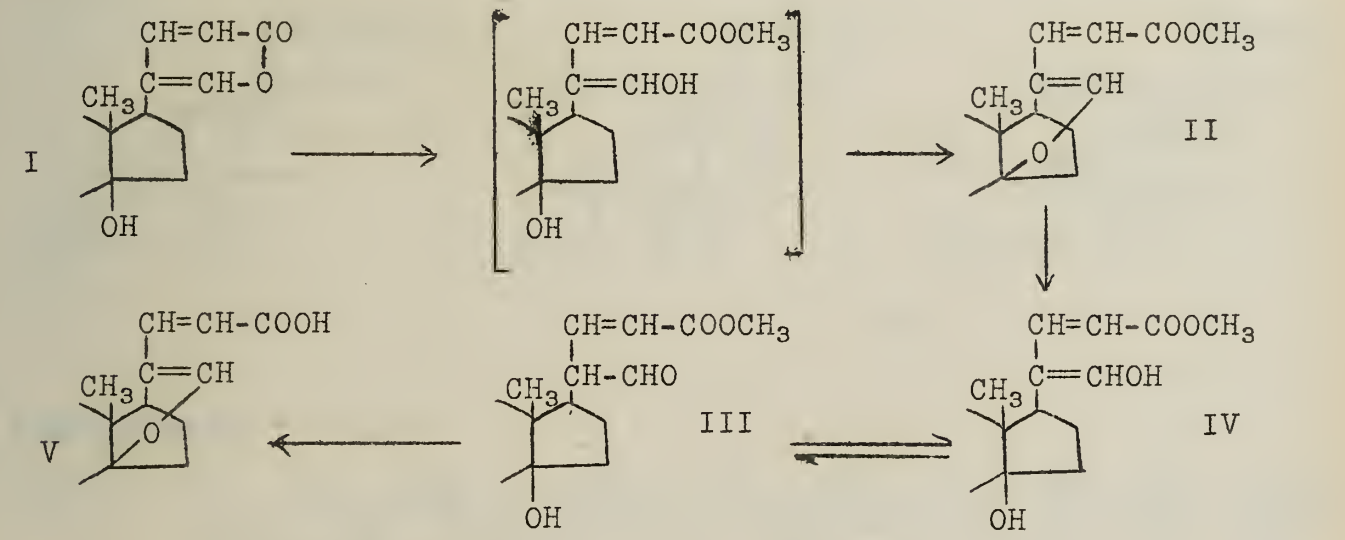
The [illegible] may be [illegible] by extraction from the [illegible]. The [illegible] of this [illegible] and the poisons [illegible] in the [illegible] with different [illegible] in conjunction with [illegible] derivatives have been [illegible] have been studied [illegible] of different [illegible]. The [illegible] of [illegible].

[illegible]

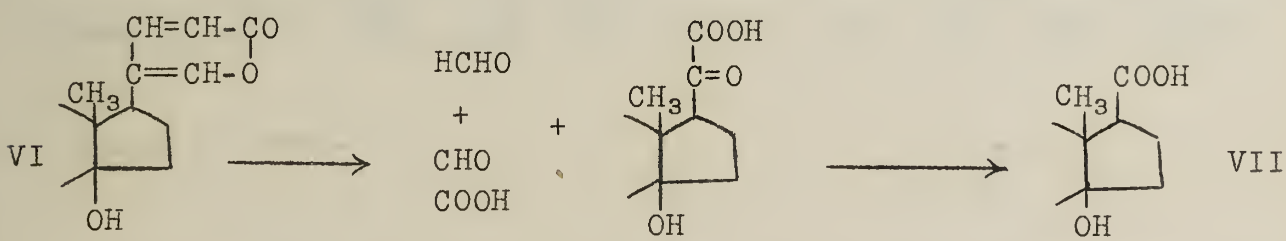
[illegible]

The reasons for this behavior are not known. Suberic acid and arginine were the other products of the hydrolysis. On hydrogenation both the anhydrogenin and the genin itself absorbed two moles of hydrogen, although the former should contain three double bonds.

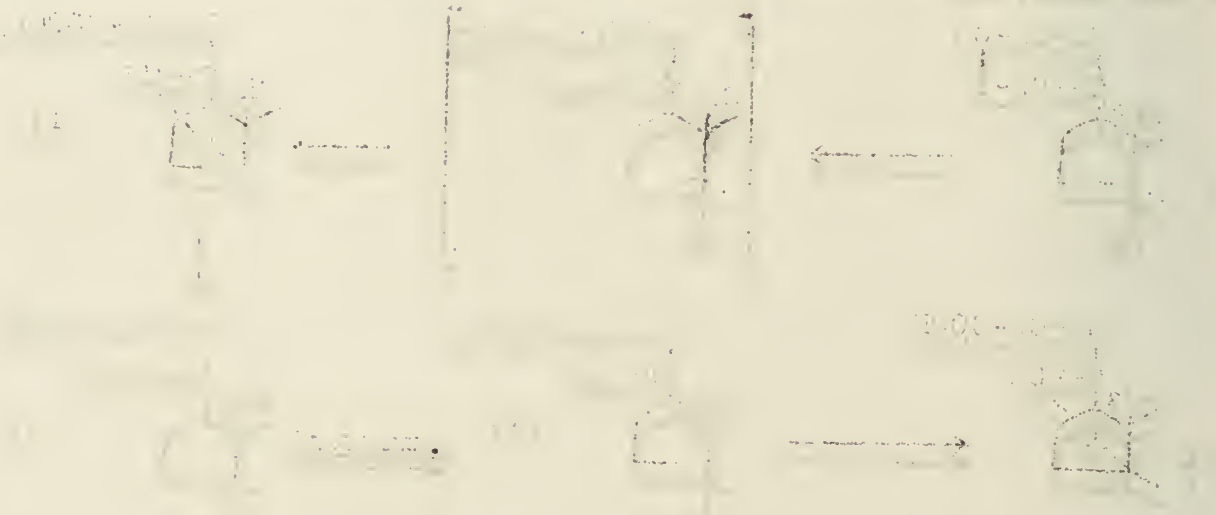
Kotake accepted Wieland's analyses and molecular formulas, but retained the name gamabufotalin, and proceeded to work out more reactions. It was found that treatment of the genin (I) with 5% KOH in CH_3OH, followed by acid, produced an alkali insoluble product (II) not containing an aldehyde group, but when this product was treated with dilute KOH, again followed by acid, aldehyde tests were obtained (III). Alkaline saponification of (II) or (III) produced an acid (V). These reactions are typical of the side chain lactone shown when an hydroxyl group is present on C_{14}, and have been studied extensively in other series. This same side chain is also present in bufotalin, and is apparently closely connected with the physiological activity of the material.



The ozonization products were also investigated. Diacetylgamabufogenin yielded formaldehyde, glyoxylic acid, and a new acid called by Kotake diacetyletiogamabufotalinic acid (VII). This seems to confirm the side chain structure, and the work of Wieland does not conflict with this.

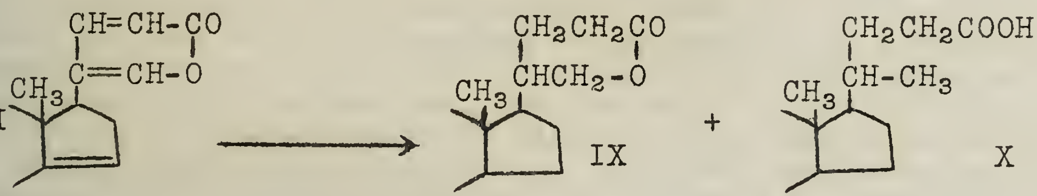


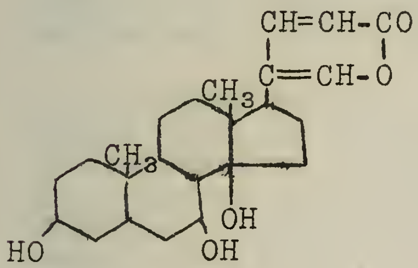
Treatment of the genin with conc. HCl yields the anhydrogenin (VIII). This may be hydrogenated to two products, IX, and a compound X which is taken to be a dihydrocholanic acid, although there seems to be no particular evidence for this. The formation of the anhydrogenin agrees with a C_{14}-OH. The two methyl groups are placed in the usual sterol positions, but it remains to place the two secondary hydroxyl groups. One is placed at C_3 by analogy with other sterols and since the C_{11}-OH acetylates with some slight difficulty while the C_7-OH



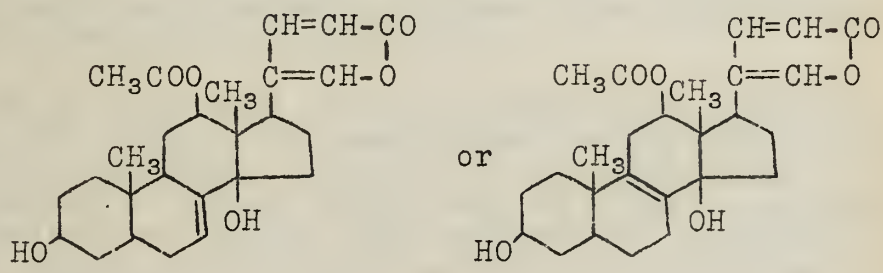
acetylates easily, the remaining hydroxyl is placed in the 7 position, the final formulation being XI. The Hammarsten reaction apparently precludes the possibility of a C_{12}-OH. The position of conjugation of the suberyl-arginine remainder in the toxin is not known, but it very probably involves a tertiary hydroxyl group.

A number of other toad poisons have been isolated, but with the exception of bufotalin and cinobufagin (XII) their structure and identity is still fairly uncertain.

VIII  IX + X



XI



XII

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Wieland et al., Ber., <u>46</u>, 3315 (1913); ibid., <u>55</u>, 1789 (1922); ibid., <u>64</u>, 2099 (1931); Sitzungsber. d. Bayr. Ak. Wiss., 329 (1920 Ann., <u>481</u>, 215 (1930); ibid., <u>493</u>, 272 (1932); ibid., <u>513</u>, 1 (1934); ibid., <u>517</u>, 22 (1935); ibid., <u>524</u>, 203 (1936); ibid., <u>528</u>, 234 (1937).

Tschesche et al., Ber., <u>68</u>, 1998 (1935); ibid., <u>69</u>, 2361 (1936).

Reported by E. C. Horning
March 8, 1939

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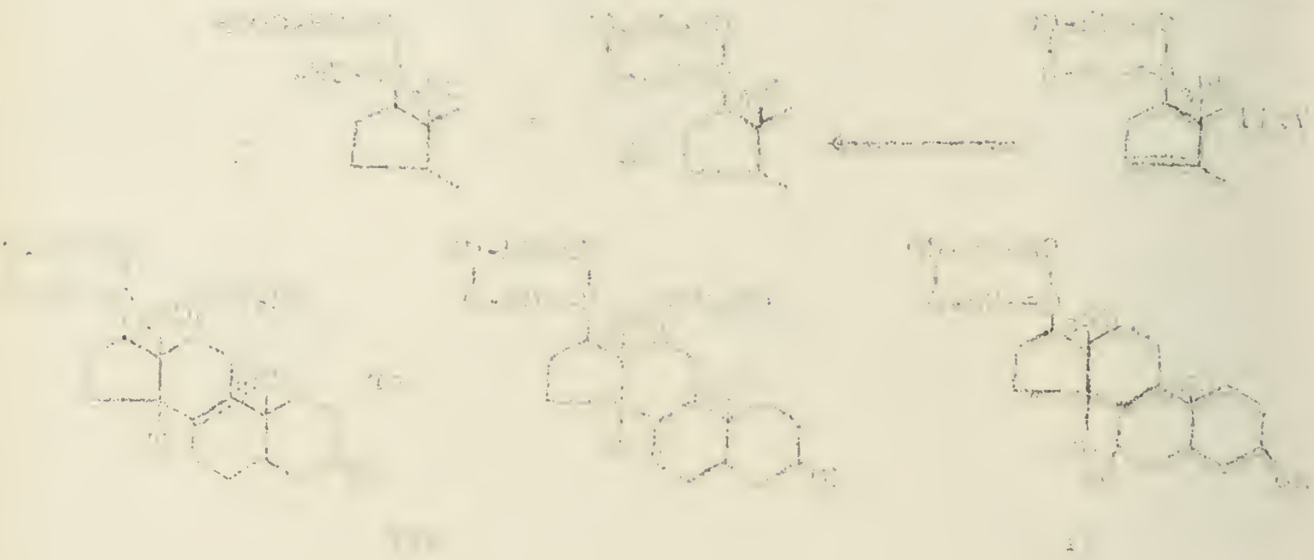

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THE FORMATION OF SULFUR-CONTAINING RINGS

G.M.Bennett -- Sheffield, England
Müller and Schütz -- Vienna

Investigations into the nature of cyclic sulfides were initiated by Mansfield in 1886. He obtained (5) a trimer of thioformaldehyde and also ethylene and propylene polysulfide polymers believed to be cyclic and to have compositions corresponding to $(C_2H_4)_3S_3$ and $(C_3H_6)_3S_3$. Von Braun's studies (4) of polymethylene monosulfides placed especial emphasis upon the nature of ring closures involving the sulfur atom. P. C. Ray and his students in Calcutta have made contributions to the knowledge of polymethylene polysulfide rings(7). Since 1927 Bennett has studied extensively the penthiane (pentamethylene sulfide) (2a) series. He has also measured (2d) the rate of formation of various sulfide rings and has begun recently the study of large ring monosulfides (2e). His work has been supplemented considerably by that of Müller and Schütz (6) in Vienna. Emmet Rèid investigated the cyclic and chain polymers derived from ethylene mercaptan and a number of polymethylene halides (8).

In general the ease of formation of sulfur-containing rings varies with the size of the ring in the same manner as does the ease of formation of alicyclic compounds. As would be predicted, the cyclizations are accompanied in almost every case by linear polymerizations. The stereochemistry of sulfur rings appears to be normal. Bennett has found, for example, that 4-aryl penthianol sulfoxides exist in cis and trans forms (2a).

Monosulfide rings have been made by the following reactions:

I. $$(CH_2)_n\begin{matrix}X\\X\end{matrix} + (NaHS + NaOEt)\ (dry) \longrightarrow (CH_2)_nS \quad (3)$$

$$+ K_2S \text{ or } Na_2S \longrightarrow (CH_2)_nS \quad (6)$$

$n = 3,4,5,6,12,13,14;\quad X = Cl,Br,I$

The structure of the monosulfide rings has been demonstrated by the following cleavage (6):

$$2\ (CH_2)_nS \xrightarrow{xs\ CH_3I} [(CH_2)_nSCH_3]I + I(CH_2)_nI + [(CH_3)_3S]I$$

$$I(CH_2)_nI + 2\ C_6H_5ONa \longrightarrow C_6H_5O(CH_2)_nOC_6H_5$$

II. 

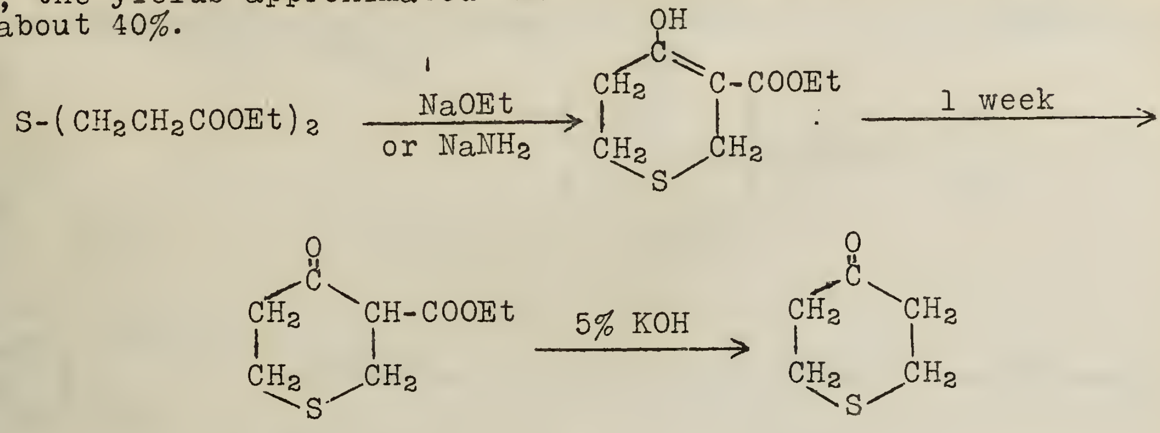
$n = 1,2,\text{or } 3$ $\quad$ 5,6,or 7 membered rings
$m = 0,\text{or } 1$ $\quad$ were formed

Two factors should influence the yield of a ring closure of this type (4b):

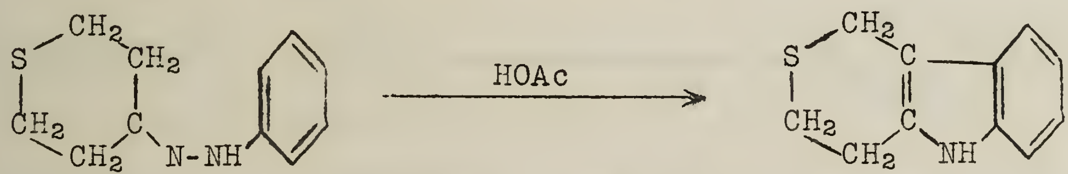
a. The size of the ring.

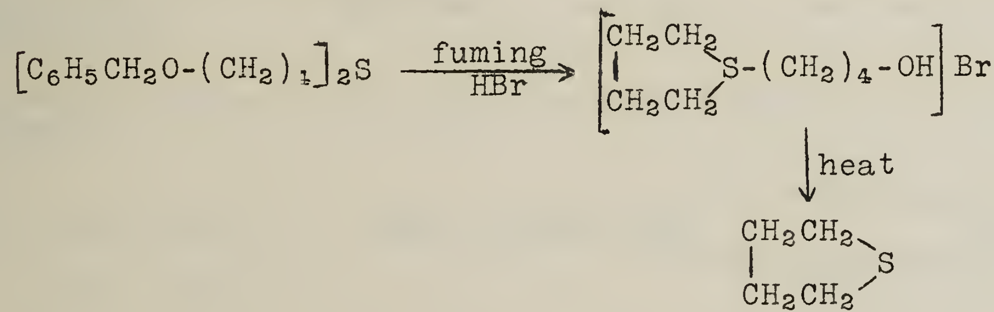
b. The position of the sulfur atom; i.e. attached directly or indirectly to the aromatic ring.

Von Braun found factor b to be the more important (4b). When m = 1, the yields approximated the theoretical while when m = 0 they were about 40%.

III. 

The penthianone and the β-keto ester may serve as starting materials for many syntheses involving the penthiane nucleus (2a). The phenyl and p-bromophenylhydrazones of penthianone rearrange in hot acetic acid to the penthiene-indoles.



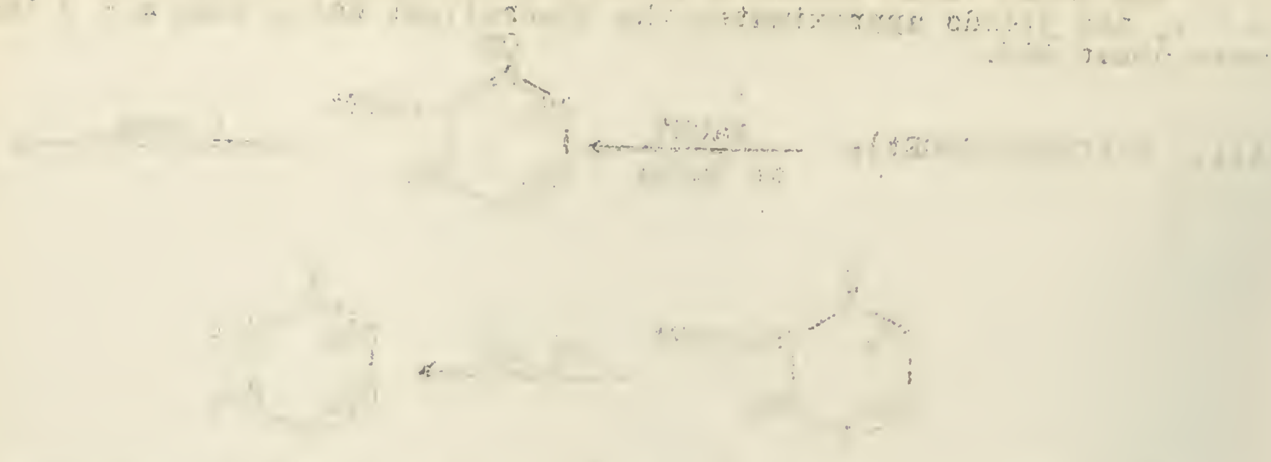
IV. 

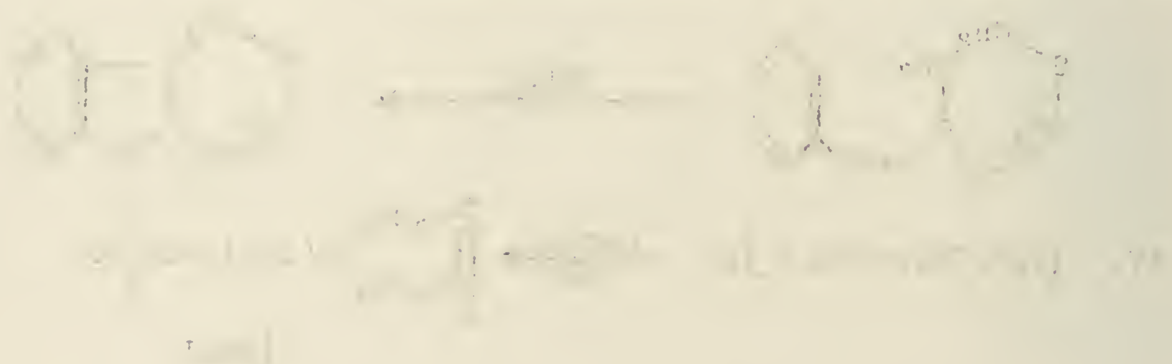
This reaction (2b) illustrates the extraordinary ease of formation of five membered rings. With $C_6H_5CH_2O-(CH_2)_n\ _2S$, where n = 3 or 5, fuming HBr leads to the straight chain dibromoalkyl sulfide.

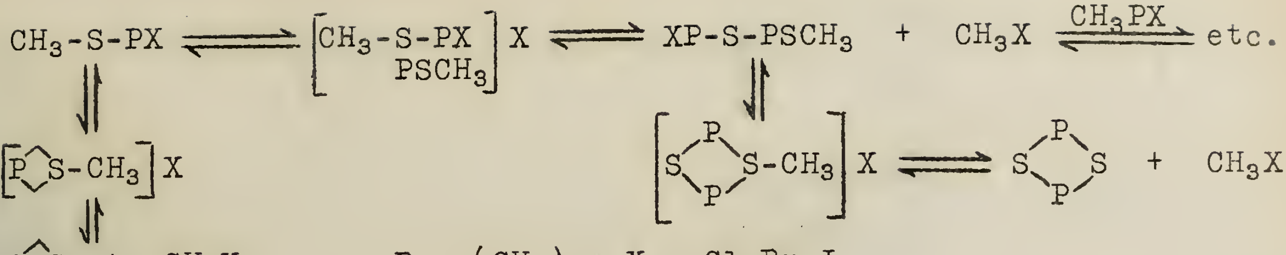
V. $Cl(CH_2)_n\text{-}S\text{-}R \xrightarrow[\text{dil. soln.}]{\text{heat}} \left[(CH_2)_n\text{-}S\text{-}R\right]Cl \xrightarrow{\text{heat}} (CH_2)_nS + RCl$

$n = 4, 5, 6, 14, 16$
$R = CH_3, C_2H_5, C_6H_5$

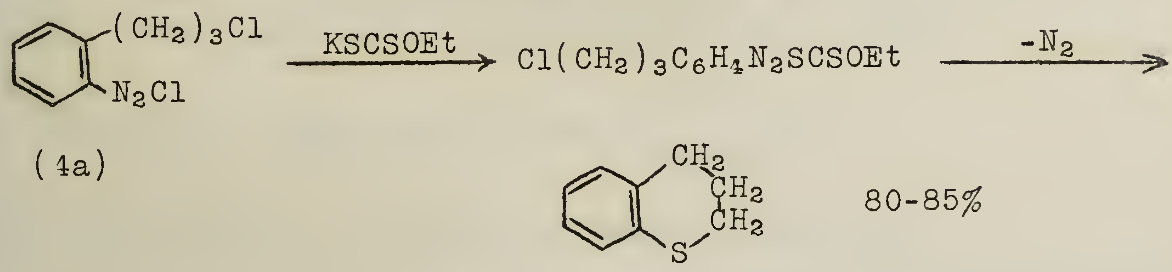
Bennett has shown (2d) that the rate of ring closure is decrease by a factor of approximately 75 as the size of the ring is increased from five to six to seven members. A change of R from CH_3 to C_2H_5 diminishes the rate by one-third. When n = 14,16, boiling acetophenone was used as the solvent. The addition of NaI was found to be advantageous. The alkyl iodide is formed slowly; the ring is closed; and the CH_3I is liberated. Bennett has suggested (2e) a mechanism to account for the various cyclic and linear products obtained in reactions of type V:





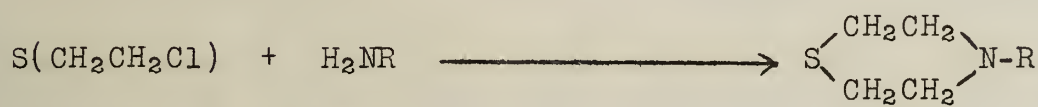


$P = (CH_2)_n$; X = Cl,Br,I

VI. 

(4a)

80-85%

VII. 

R = C_6H_5, CH_3, C_2H_5, etc.

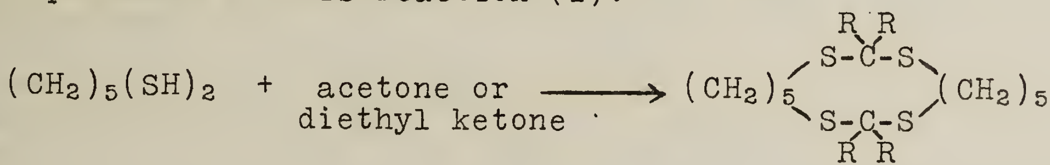
Reference 8a gives a comprehensive account of the reactions of "mustard gas".

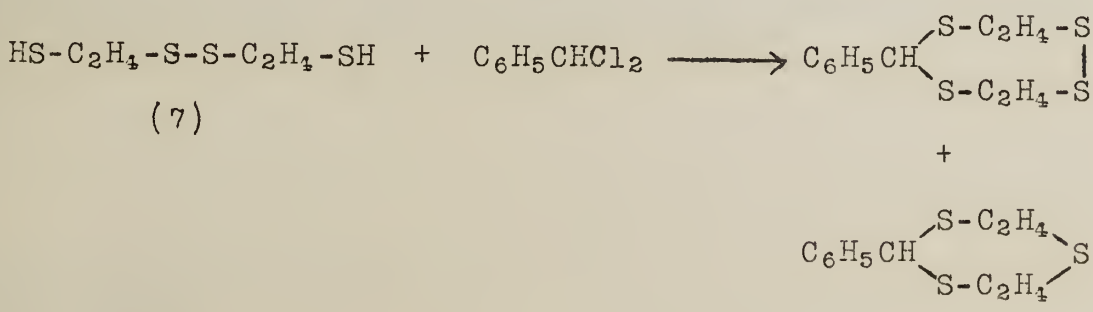
Di- and polysulfide rings have been prepared by the following reactions:

VIII. 

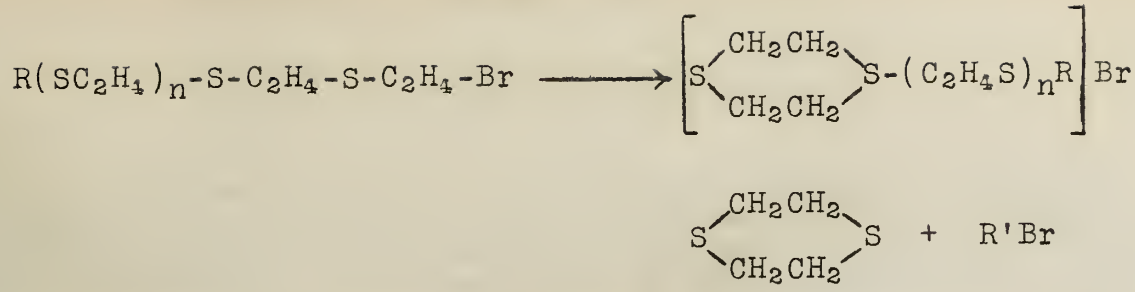
o-, m-, and p-

Cis-trans isomerism, contrary to prediction, could not be detected in the products of this reaction (1).

IX. 

X. 

(7)

XI. 

Only ethylene sulfide polymers containing halogen decompose in this way (2c). Those containing no halogen will give dithiane when heated with HBr. They may have as end groups CH_2OH or $CH=CH_2$.

XII. 

XIII. $NaSCH_2CH_2SNa$ + $(CH_2)_nBr \longrightarrow (CH_2)_2S_2(CH_2)_n$

$n = 1,2,3,4,5,6$ and/or $[(CH_2)_2S_2(CH_2)_n]_2$

The 8 and 9 membered rings (n = 4,5) are not formed. The dimer is obtained in these cases. Both dimer and monomer are found when n = 3 (8b).

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2. a. Bennett et al., J. Chem. Soc., 1927, 194; ibid., 1929, 2829, 2832.
   b. Bennett and Hock, ibid., 1927, 477.
   c. Bell, Bennett and Hock, ibid., 1927, 1803.
   d. Bennett, Heathcoat and Mosses, ibid., 1929, 2567; Bennett and Turner, ibid., 1938, 813.
   e. Bennett and Gudgeon, ibid., 1938, 1891.
3. Bost and Conn, Oil and Gas J., 32, No. 3, 17 (1933); C.A. 27, 5323 (1933); Chem. Zentr., 33II, 2673 (1933).
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6. Müller and Schütz, ibid., 71, 692 (1938).
7. Ray et al., J. Chem. Soc., 125, 1141 (1924).
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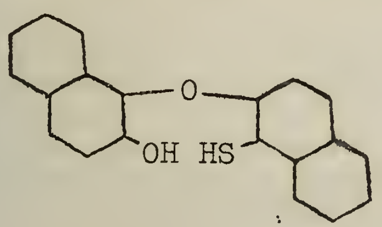
Reported by S. C. Kelton
March 8, 1939

REARRANGEMENTS OF ARYL SALICYLATES AND

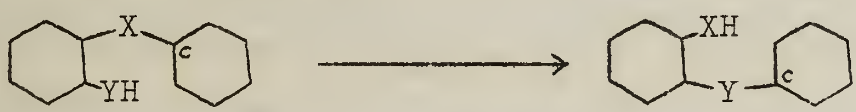
COMPOUNDS OF SIMILAR CONSTITUTION

Smiles -- King's College, London

The accidental discovery by Warren and Smiles in 1930 that 1-sulfhydryl-2'-hydroxy-2,1'-dinaphthyl ether (I) was rearranged by heat or alkali into 2,2'-dihydroxy-1,1'-dinaphthyl sulfide (II) led Smiles to investigate the possibility of rearrangements in compounds

I  II

of similar constitution. Smiles concluded that the above conversion was the result of an intramolecular change, and after numerous studies has found that many compounds of the general type III can undergo such rearrangements to give IV. All of these conversions were effected by

III  IV

heat and alkali, or, in some cases, by heat alone.

The results of these studies are summarized in the following table:

If YH is:	X may be:
1. NHAc	SO_2,SO,S, or O
2. OH (alkyl)	SO_2,SO, but not S
3. OH (aryl)	SO_2,CO_2, but not SO or S
4. NH_2 (aryl)	SO_2,(SO?),O, but not S
5. SH	O
6. $CONH_2$	O
7. CONHAc	O,SO_2
8. SO_2NH_2,SO_2NHR	O

The chief conditions controlling these rearrangements are as follows:

1. The positive character of the carbon atom c (see figures III and IV). An increase in the positivity of c should favor the conversion, not only by lessening the stability of the linkage with the positive group X, but also by increasing the demand for the electron supply offered by Y.

2. The character of the medium in which the rearrangement is effected, as expressed by the tendency to remove a proton from YH.

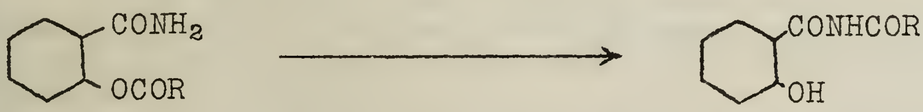
3. The character of the YH group, as shown by the instability of the electron system of Y or its capacity to act as a donor to meet the demands of the positive carbon atom c.

Although all of the above rearrangements have involved mainly

aromatic nuclei, with the exception of type 2 of the above table, it should be mentioned that at least one other example has been found in the aliphatic series. Thus p-nitrobenzenesulfonylacetanilide V yielded the sulfinic acid VI.

$$\text{V}\quad \begin{array}{l} CH_2SO_2C_6H_4NO_2 \\ | \\ CONHC_6H_5 \end{array} \longrightarrow \begin{array}{l} CH_2SO_2H \\ | \\ CO\text{-}N\text{-}C_6H_4NO_2 \\ \quad\;\; C_6H_5 \end{array} \quad \text{VI}$$

Probably the first known conversion of this general type was the observation by Böttcher in 1883 that the reduction of O-benzoyl-o-nitrophenol yielded not the corresponding amino compound, but N-benzoyl-o-aminophenol. More recently it has been found that O-acylsalicylamides are transformed by heating above their melting points into the corresponding N-acyl isomers. It is interesting to note



that this reaction is reversible, the N-acylsalicylamides being converted into the O-acyl compounds on boiling with glacial acetic acid. No reversibility has been observed in the preceding rearrangements.

In conclusion, it may be stated that these reactions probably have very little preparative value, although fairly good yields were obtained in some cases. The work in this field is being continued.

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Roberts and de Worms, J. Chem. Soc., 1934, 727; ibid., 1935, 196,1309.
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Böttcher, Ber., 16, 629 (1883).
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Ransom, ibid., 31, 1060 (1898); ibid., 33, 199 (1900).
Auwers, ibid., 37, 3903 (1904).

Reported by S. L. Scott
March 15, 1939

THE STRUCTURE OF ROTTLERIN

Brockmann and Maier -- Göttingen
Robertson -- Liverpool

Rottlerin, $C_{30}H_{28}O_8$, is the active anthelmintic of the drug "kamala" obtained from the fruit glands of the Oriental Mallotus phillipinensis; in India this reddish-brown pigment is also used as a silk dye. The structure (I) has been deduced from the following reactions:

A. Formation of pentaacyl or pentamethyl derivatives.

B. Absorption of two mols of hydrogen to give tetrahydrorottlerin (II), a much more stable compound.

C. Inner condensation upon heating to isorottlerin (III) of the same composition.

D. Scission products of rottlerin, tetrahydrorottlerin and isorottlerin.

1. Warming with weak alkali.

a. Rottlerin gave C-methylphloroglucinol and rottlerone (IV). Dilute sodium hydroxide gave some benzaldehyde also; zinc dust and dilute potassium hydroxide gave C-dimethylphloroglucinol and other scission products.

b. Tetrahydrorottlerin gave C-methylphloroglucinol and tetrahydrorottlerone (V).

2. Heating with concentrated alkali.

a. Rottlerin gave phloroglucinol, acetic, benzoic, and cinnamic acids.

b. Tetrahydrorottlerone gave only β-phenylpropionic acid and 5,7-dihydroxy-2,2-dimethylchromane.

3. Heating rottlerin with diazoaminobenzene gave 3-acetyl-5-methyl-2,4,6-trihydroxyazobenzene (VI).

4. Heating in vacuo: rottlerin and isorottlerin both gave 2-methylphloroacetophenone.

E. Miscellaneous

1. Isorottlerin absorbs only 1 mole of hydrogen with palladium catalyst.

2. Ozonization of rottlerin gave 0.9 mole of benzaldehyde; isorottlerin gave no benzaldehyde.

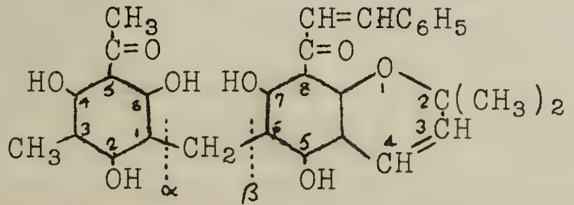
3. Oxidation with ozone-$KMnO_4$ gave 0.2 mole of acetone from rottlerin and 0.48 mole of acetone from isorottlerin.

4. Oxidation of rottlerin with $KMnO_4$ gave 1 mole of benzoic acid.

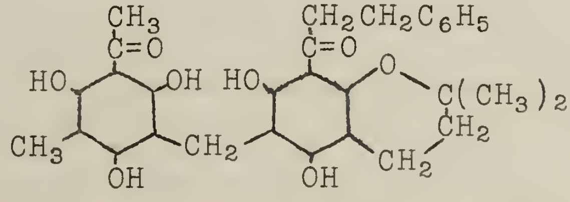
5. Alkaline hydrogen peroxide gave cinnamic acid.

6. Other oxidative degradation products are acetic acid and succinic acid.

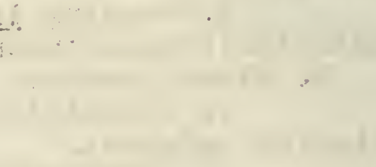
The structure assigned is 6-(2,4,6-trihydroxy-3-methyl-5-acetylbenzyl)-2,2-dimethyl-5,7-dihydroxy-8-cinnamoyl-Δ^3-chromene (I).



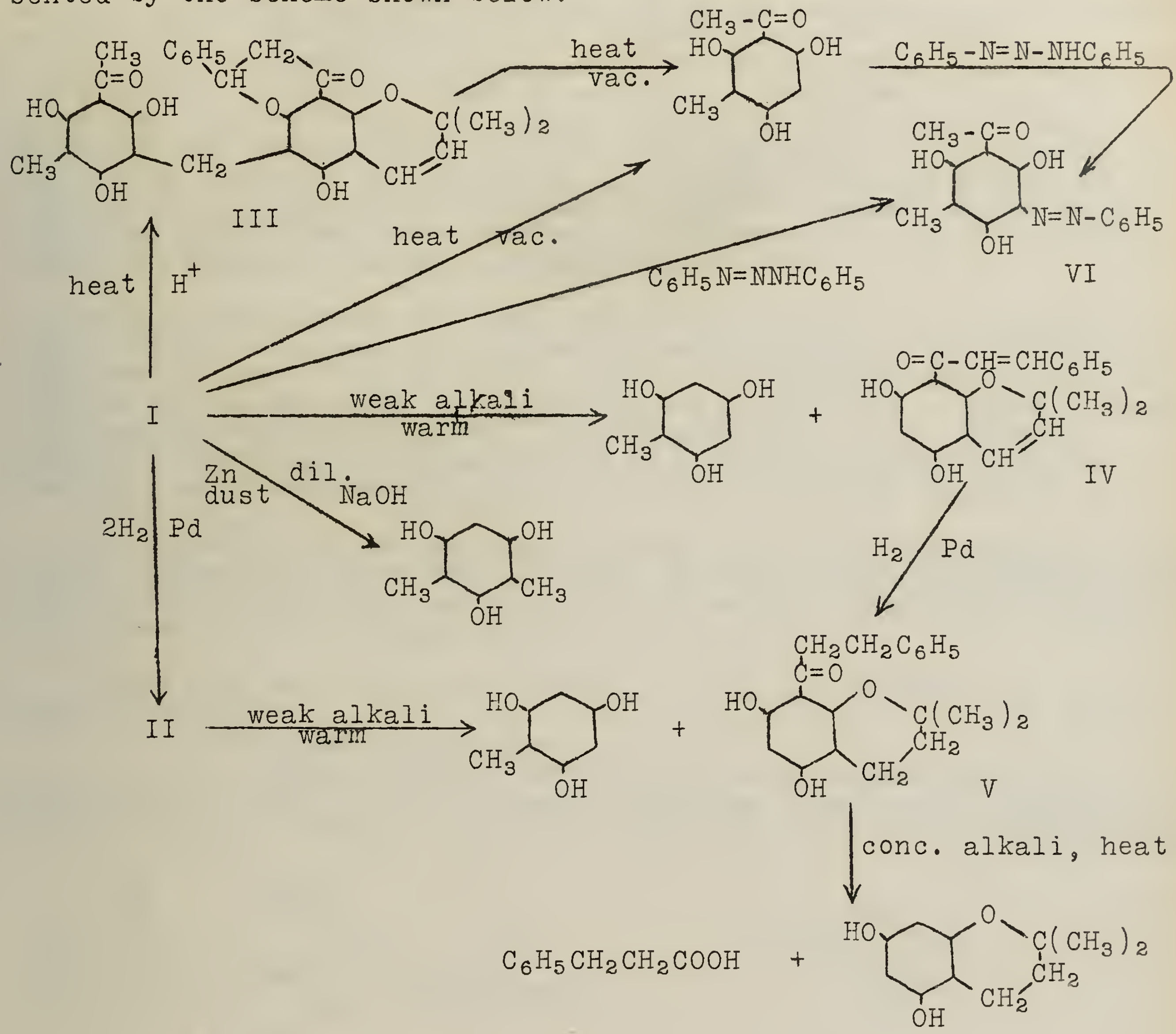
Rottlerin (I)



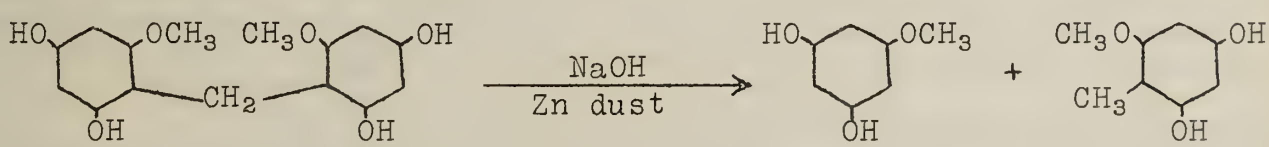
Tetrahydrorottlerin (II)



On this basis the transformations indicated above may be represented by the scheme shown below.



Boehm found that heating bismethylphloroglucinol or similar compounds with sodium hydroxide, or sodium hydroxide and zinc dust, cleaved them at the methylene bond. For example:



Further, any phloroglucinol nucleus attached to other structures by a methylene group yielded phloroglucinol or methylphloroglucinol. By analogy, then, I should give 3-methyl- and 3,5-dimethylacetophenone by cleavage at α and β . However, Brockmann and Maier have shown that 2 hours heating with 2N sodium hydroxide removes the acetyl radical from phloroacetophenone. This, then, explains the isolation of only the methyl- and dimethylphloroglucinol upon heating rottlerin or tetrahydrorottlerin with alkali. The ease of cleavage at the methylene group of the bisphloroglucinols is illustrated by the fact that

warming them with diazoaminobenzene gives the trihydroxyazobenzene in good yields. Hence, formation of VI under these mild conditions proves, beyond reasonable doubt, that the acetyl group is present in the original rottlerin. That it was not a larger acyl group, which could scarcely be decided by elementary analysis on such a large molecule, was indicated by the excellent agreement of the absorption spectra of synthetic 2,4,6-trihydroxy-3-methyl-5-acetylazobenzene with that of VI. In addition a mixed melting point showed no depression, while one with VI and the azo compound derived from synthetic methylphloropropiophenone showed a depression of 10°.

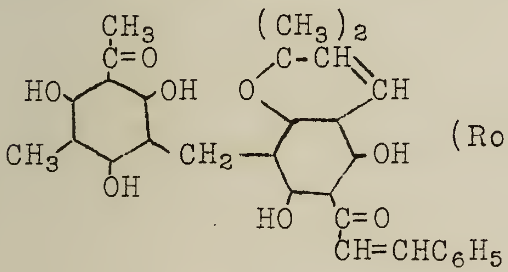
Since ozonization of I gave essentially one mole of benzaldehyde while similar treatment of II gave no benzaldehyde, a benzylidene group was inferred. That this is part of a cinnamoyl residue was indicated by the fact that hot concentrated alkali upon I gives cinnamic acid whereas rottlerone gives β-phenylpropionic acid. Warming rottlerin with dilute sodium hydroxide produces some benzaldehyde (Perkin); such behavior is characteristic of hydroxychalcones.

The behavior of tetrahydrorottlerone with hot concentrated alkali strongly supports the structure V; the 2,2-dimethyl-Δ^3-chromene unit has been found in a number of other natural compounds, particularly those of the rotenone series.

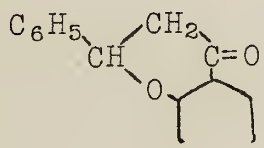
There are two lines of reasoning in deciding between the structures I and VII.

A. Brockmann and Maier

Isorottlerin is undoubtedly an hydrogenated flavone formed by the addition of a phenolic hydrogen atom to the α-position in the cinnamoyl residue (see VIII) since only 1 mole of hydrogen was



VII
(Robertson)



VIII

easily absorbed, ozonization gave no benzaldehyde, and sublimation gave 3-methylphloroacetophenone. Yet, if the structure were that of VII there would be <u>two</u> isorottlerins whereas only one was isolated.

B. Robertson

Both rottlerone and tetrahydrorottlerone are sparingly soluble in dilute aqueous sodium hydroxide. Since 2,2-dimethyl-5,7-dihydroxy-8-acetylchromane is readily soluble in 4% sodium hydroxide, one might logically infer that the cinnamoyl group is then in the 6-position.

The argument of Brockmann and Maier is probably preferable.

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Reported by R. O. Sauer
March 15, 1939

THE "OXIDIZING ACTION" OF ALKALIES

Lock -- Vienna
E. E. Reid -- Baltimore, Md.

In 1832, Wöhler and Liebig[13] obtained benzoic acid from benzaldehyde on fusion with potassium hydroxide. A few years later Dumas and Stas[4] discovered the reaction:

$$CH_3CH_2CH_2CH_2OH + NaOH \xrightarrow{fusion} CH_3CH_2CH_2C(ONa){=}O + 2\ H_2$$

They found that the above reaction is best for high molecular weight alcohols; e.g. they obtained palmitic acid from cetyl alcohol by sodium hydroxide fusion at 250° in good yields. Wöhler and Liebig formulated their theory, whereby organic compounds under the influence of alkalies take over the oxygen from the water which is present, and are oxidized with the liberation of hydrogen, which comes jointly from the water and the carbon compound. Hence:

$$C_2H_5OH + H_2O \xrightarrow{NaOH} CH_3COOH + 2\ H_2$$

This old theory was accepted until 1918, when Carrol[3] introduced his mechanism for the conversion of alcohol to the salt of acetic acid in the presence of soda-lime. The reaction takes place in three stages; the first stage is the dissociation of alcohol to aldehyde and hydrogen in the presence of caustic soda as catalytic reagent:

1st stage: $C_2H_5OH \longrightarrow CH_3CHO + H_2$

2nd stage: $CH_3CHO + \text{caustic soda} \longrightarrow CH_2{=}C{=}O + H_2$

3rd stage: $CH_2{=}C{=}O + NaOH \longrightarrow CH_3COONa$

The intermediate ketene was not proven to be present.

Fry[5], who studied the alkali fusion of a series of aliphatic compounds, concluded that the reaction involved the acidic dissociation of the alkalies and the replacement of hydrogen or methyl radical by -ONa radicals.

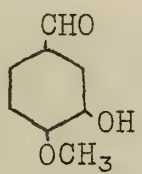
$$HONa \longrightarrow H\cdot + \cdot ONa$$

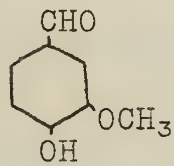
In the case of the oxidation of hydroxylated toluene, benzyl alcohol or benzaldehydes the usual oxidizing agents fail to work. By their use no acid is obtained while a stronger oxidation causes the destruction of the benzene ring. The reason for this phenomenon must be due to the greater resista ce of the functional group to the oxidizing agents in the presence of a hydroxyl group on the ring, and also to the lessened resistance of the hydroxy-carboxylic acids against oxidizing agents.

Lock[10] studied the fusion with alkali of these same compounds. He found that potassium hydroxide reacts quite rapidly even at 105-110° with salicyl aldehyde converting it quantitatively into salicylic acid with the evolution of one mole of hydrogen. The *m*- and *p*-hydroxy compounds on fusion decompose similarly into acid and hydrogen. Unlik the ortho derivative the *m*- compound begins to react only at about

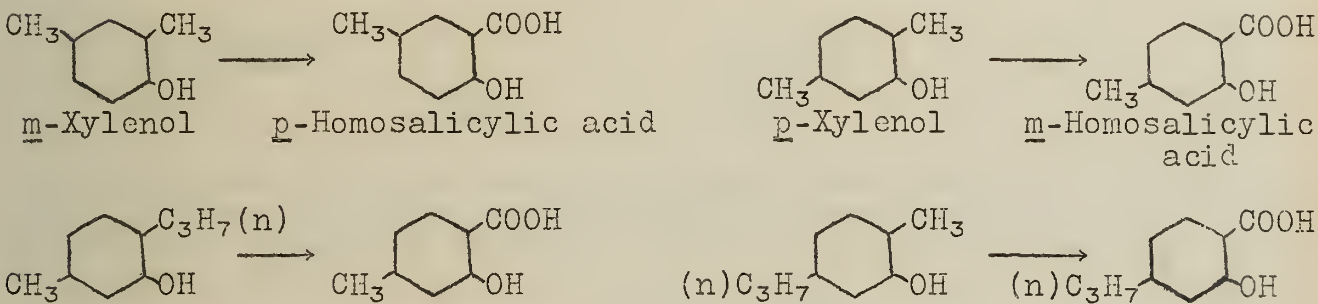
190°, due probably to the tendency at low temperature for a Cannizzaro reaction to take place and at 190° the potassium hydroxide reacts to oxidize the alcohol. That there is not first a Cannizzaro reaction with the *ortho* compound was indicated by the fact that saligenin, as well as the corresponding *meta* and *para* alcohols, and potassium hydroxide do not react below 165°. The old rule that a phenolic hydroxyl group prevents the disproportionation into alcohol and acid, holds, therefore, only when the hydroxyl group is in the *ortho* and *para* position to the -CHO group. Substituted *m*-hydroxybenzaldehydes gave similar results.

Lock found that on the fusion of *p*-$HO-C_6H_4-CHO$, 3,4-$(OH)_2C_6H_3CHO$ and vanillin (I), hydrogen is evolved at 110°. Isovanillin (II) does not evolve hydrogen below 190°.

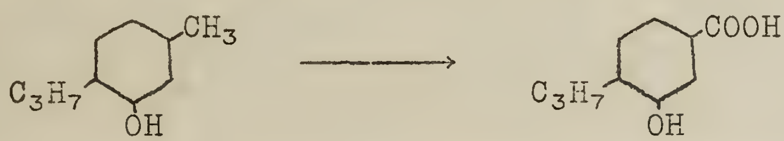
II 

 I

Jacobsen[8] reported in the literature the following fusions:

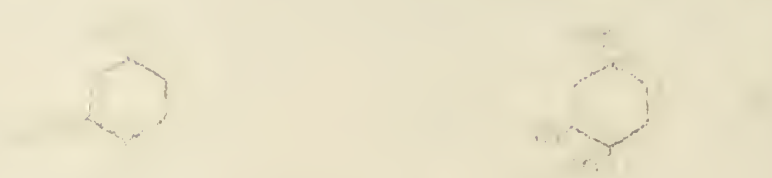


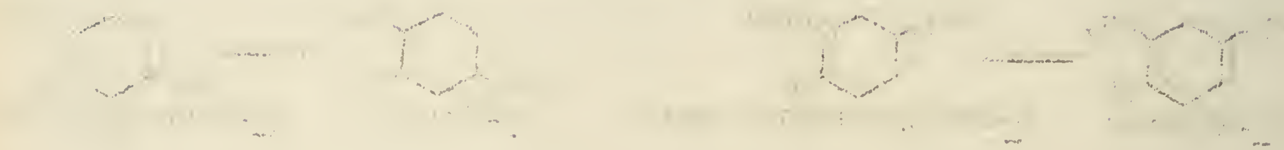
From these data, he gave the rule that the side-chain nearest the OH group is the one that undergoes oxidation in alkali fusion. However, Barth[1] showed that the methyl group is the one which is oxidized in thymol :

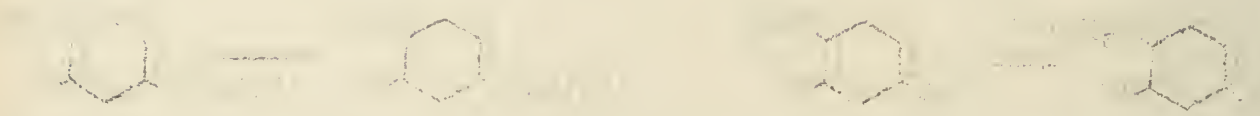


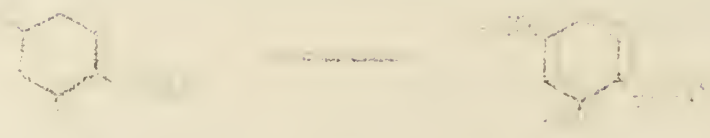
Lock found that when he fused *o*-cresol with alkali in a nickel crucible, a rapid reaction occurred at a temperature of 300-310° and he obtained a 50% yield of salicylic acid in one hour and about 80% yield after five hours. Carrying out the same procedure in a closed silver crucible in an atmosphere of nitrogen, he obtained neither hydrogen nor salicylic acid and completely recovered *o*-cresol. In a current of air and the same apparatus, hydrogen and salicylic acid were obtained. Some of the salicylic acid had undergone CO_2 splitting

The mechanism of the above reaction is similar to the mechanism of the oxidation of the substituted benzaldehydes and benzyl alcohols; that is, a hydroxylation of the methyl group with a simultaneous dehydrogenation.









$$KO\text{-}C_6H_4\text{-}CH_3 + 3\ HOK \longrightarrow KO\text{-}C_6H_4\text{-}C(OK)_3 + 3\ H_2$$

$$KO\text{-}C_6H_4\text{-}C(OK)_3 + HOH \longrightarrow KO\text{-}C_6H_4\text{-}COOK + 2\ KOH$$

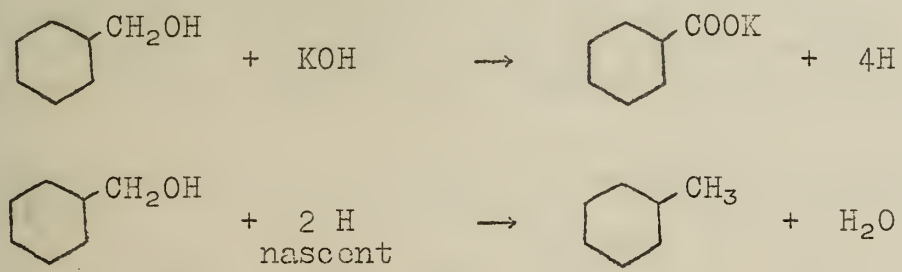
$$KO\text{-}C_6H_4\text{-}CH_2OK + 2\ HOK \longrightarrow KO\text{-}C_6H_4\text{-}C(OK)_3 + 2\ H_2$$

$$KO\text{-}C_6H_4\text{-}CHO + HOK \longrightarrow KO\text{-}C_6H_4\text{-}COOK + H_2$$

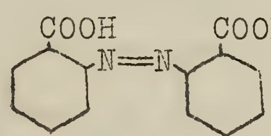
Alkali fusions of the sodium and potassium salts of benzoic acid show a tendency of splitting off CO_2 as the temperature is raised; thus at 400° sodium benzoate was 100% decomposed into CO_2 and benzene.

Toluene and mesitylene were recovered unreacted even at temperatures as high as 500°.

The fusion of benzyl alcohol gave toluene along with the benzoic acid. This is explained by:



With concentrated sodium hydroxide, Maier obtained with the three nitrobenzaldehydes what he believed was a mixture of azo- and nitrobenzoic acids. Lock showed that azobenzoic acid is formed from the o-nitro compound



and the corresponding azoxy compound from the meta and para. He proved the latter by synthesis. Similarly o-nitrobenzyl alcohol gave the azobenzoic acid while the corresponding m- and p- gave the azoxy. It is a two step reaction: (1) Dehydrogenation of the $-CH_2OH$ group; (2) Reduction of the nitro group by the liberated hydrogen.

In the study of the reaction of halogen substituted benzyl alcohols, here again he found a two stage reaction where the first stage is the same as above and the second is the substitution of the halogen by the liberated hydrogen.

Sodium hydroxide and lithium hydroxide react in the same way as the potassium hydroxide, but higher temperatures are required. Even barium hydroxide dehydrated at 120° can effect oxidation. $NaNH_2$ could not be made to react with the compounds.

In contrast to the aromatic methyl compounds, the aliphatic methyl compounds give methane, as shown by Fry[5]:

$$R\text{-}CH_3 + KOH \longrightarrow ROK + CH_4$$

He shows that ethyl alcohol, acetaldehyde and acetone fused with potassium hydroxide under mild conditions give the salt of acetic acid but by more drastic action the methane is obtained:

$$CH_3CHO + KOH \longrightarrow CH_3COOK + H_2$$

$$CH_3COOK + KOH \longrightarrow CH_4 + K_2CO_3$$

Methyl alcohol does not give methane, and as shown by Reid[12] some formic acid is formed in the fusion; hence

$$CH_3OH + 2\ KOH \longrightarrow 3\ H_2 + Na_2CO_3$$

involves the formation of the intermediate formic acid which splits into CO_2 and hydrogen.

Ethanol, acetaldehyde, acetone, n-propyl alcohol, isopropyl alcohol, and tert-butyl alcohol all give sodium carbonate, methane and hydrogen as products as does glycerol, dextrose, cellulose, and other polyhydroxy compounds. Ethylene glycol, methyl alcohol, and formaldehyde give the carbonate and hydrogen. Ammonia, CH_3NH_2, $(CH_3)_2NH$, $(CH_3)_3N$, $(CH_3)_2O$, and $(C_2H_5)_2O$ resisted the action of fused alkali.

Reid[12] studied the reactions of aliphatic alcohols on fusion with alkali.

(1) $PrCH_2OH + NaOH \longrightarrow PrCOONa + 2\ H_2$

(2) $EtCH_2CH_2OH \longrightarrow Et\text{-}\underset{Bu}{CH}\text{-}CH_2OH + H_2O$

These reactions are here associated because they so frequently go on in the same mixture. In reaction (2) the attack is predominantly on the β-carbon but may also be on the α-carbon. Naturally the alcohol that is formed may also take part in the condensation; thus from butenol, a dodecanol and a hexadecanol are obtained along with an octanol, but in smaller amounts. Reaction (1) goes rapidly at about 320°. Several runs were made with ethanol. The conversion to the salt of acetic acid increased from 67% to 98.9% when the ratio of alcohol to caustic alkali was increased from one to three. The presence of water is beneficial; it suppresses reaction (2) and prevents darkening. Sodium carbonate appeared when the temperature was high or the time too long. Ethanol differed from the other alcohols in that it w s extensively dehydrated, particularly when much water was present.

In the case of anhydrous butanol, n-propyl- and 2-ethylhexanol the yield of octanol, etc., was larger when potassium hydroxide was used. With tert-butyl alcohol about one-fourth of the alkali went to the carbonate, no acid was isolated and the rest of the alcohol recovered unchanged.

The fact that sodium acetate is used as a condensing agent in Perkin's Synthesis and in acetylations, suggested that the salts that were formed in Guerbert's experiments[7] may have been responsible at least in part, for the condensations. It has been found that salts of organic acids do effect condensations according to reaction (2).

Reid ran a series of reactions with butyl alcohol and the various salts of butyric acid and found that the potassium and sodium salts of fatty acids are efficient catalysts for condensing two molecules of an alcohol into one of a higher molecular weight.

Thus alkali fusion is a very useful method of oxidizing hydroxybenzaldehydes, hydroxybenzyl alcohols, hydroxytoluenes, and other substituted aromatic compounds. It is also useful for obtaining fatty acids from aliphatic alcohols.

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Reported by J. F. Kaplan
March 22, 1939

Hönel

Phenolic resins, particularly phenol-formaldehyde resins, are far superior to natural resins for various industrial products. Up until 1880, various phenol-formaldehyde products of varying propertie were obtained but none of commercial value were synthesized.

The first commercial resin was produced by Smith in 1899. Phenol was condensed with acetaldehyde and paraldehyde in acid solution. The product was hard, brittle, and porous but it could not be moulded and so found limited use.

In 1905, Blumer, using tartaric acid as a catalyst, produced a permanently fusible, alcohol-soluble resin which was used as a shellac substitute.

The name most closely associated with phenolic resins is that of Baekeland. The Bakelite process overcame most of the difficulties encountered in earlier processes. Baekeland classified phenolic resi into two groups:

<u>Class I</u>: Permanently soluble and fusible resins of the type produced from phenol and formaldehyde in molecular proportions in aci medium. The product is acetone- and alcohol-soluble and has shellac-like properties. It is not "thermo-setting". Baekeland called these resins "Novolaks". They can often be converted to Class II resins by heating with formaldehyde.

<u>Class II</u>: Insoluble, infusible resins. Class II resins cannot be converted to Class I resins by heating with phenol. They are prepared with larger proportions of formaldehyde and basic catalysts are used.

Baekeland found that acid catalysts tend to promote formation of Novolaks whereas basic catalysts promote the formation of insolubl infusible resins almost independently of the proportions of phenol and formaldehyde used.

<u>The Bakelite Process</u>: The process usually is carried out in two or three stages the products of which are termed Bakelite A, B, and C which correspond to Lebach's "resol", "resitol", and "resit".

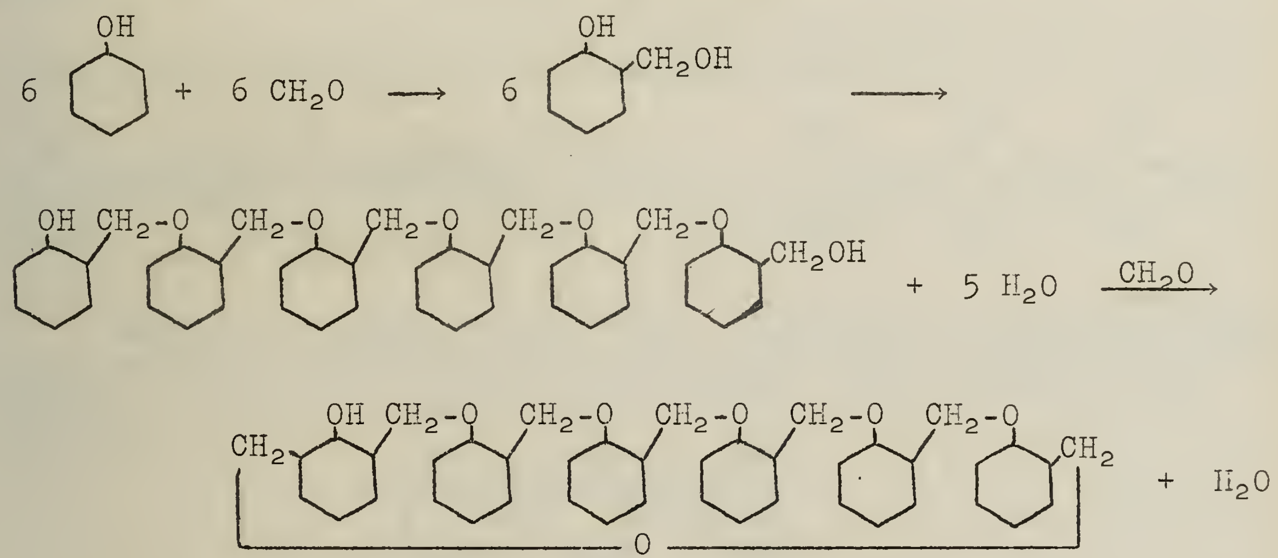
Bakelite A: Equivalent quantities of phenol and 40% formalin solution are condensed by means of a basic catalyst, usually ammonia, with or without heating. An aqueous layer separates and is removed. The residue may be liquid, pasty, or an amorphous solid, depending on conditions and the proportion of formaldehyde used, and may be converted directly to Bakelite C by application of heat and pressure. The liquid is sometimes used to impregnate articles. The coating obtained upon Bakelizing is superior to varnish. Solid A melts upon heating and is soluble in ordinary solvents.

Bakelite B: Solid A is ground and mixed with an appropriate filler and heated. The appearance of a rubbery-like stage at about 70°C. indicates its conversion to Bakelite B. It softens on heating,

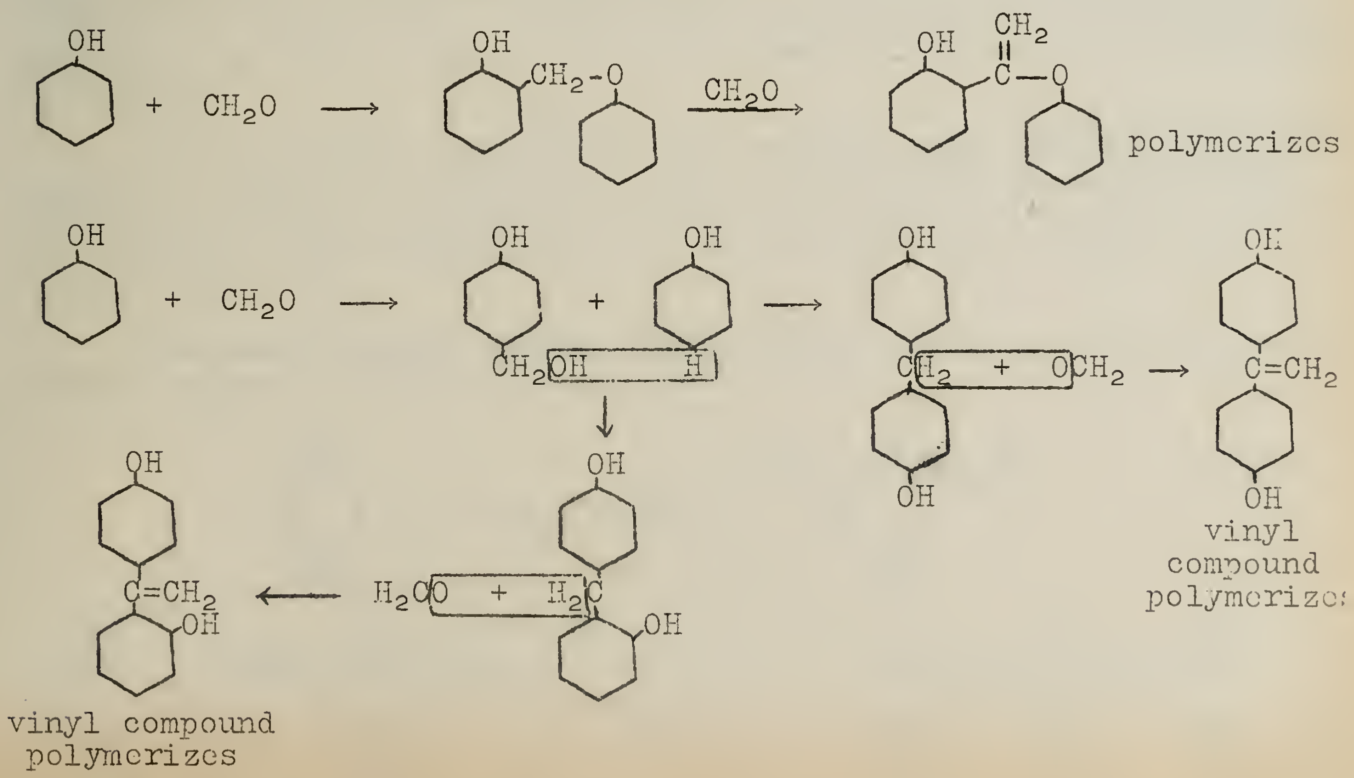
but does not melt, becomes brittle on cooling and swells in acetone. It can be stored as such, molded in a hot mould, removed from the mould and Bakelized under pressure without losing its shape to Bakelite C.

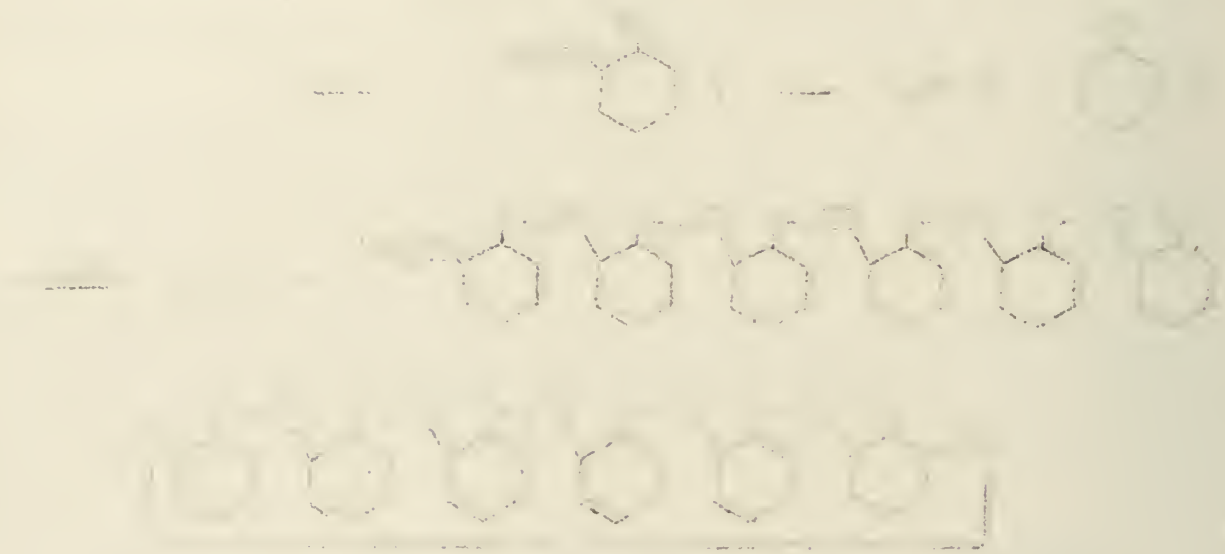
Bakelite C: The final product, Bakelite C, is always formed by application of heat under a pressure of 50-110 pounds to prevent the dissociation of formaldehyde which caused porosity in earlier resins.

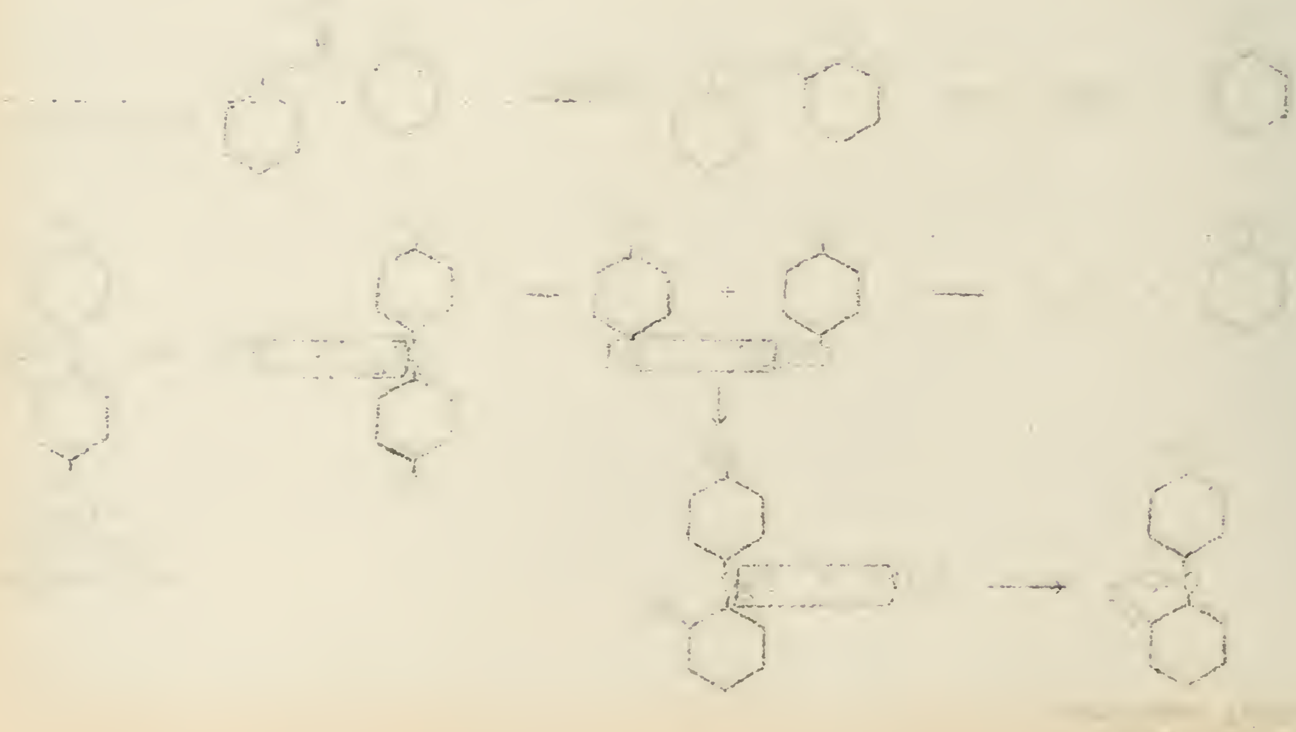
<u>Theories on the reactions between phenols and formaldehyde:</u> All theories thus far developed involve splitting out of water at some stage. Baekeland proposed the following mechanism on the basis of his synthesis of Bakelite from saligenin:



The six-membered ring then polymerizes to the infusible resin. He also proposed the following mechanisms:

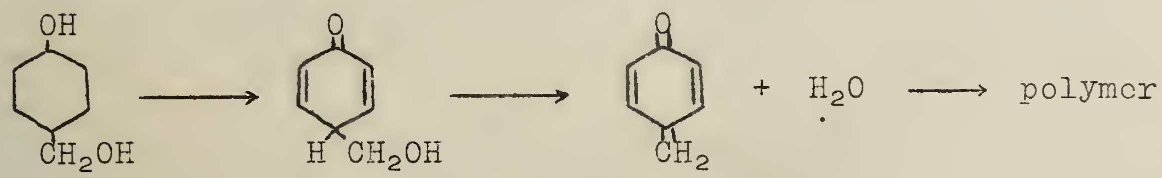






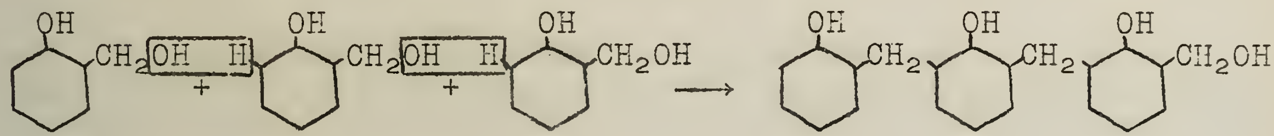
The isolation of 2,4'- and 4,4'-dihydroxyphenylmethanes in preparing the resins suggested the latter mechanism.

The following mechanism was suggested by Wohl and Mylo:

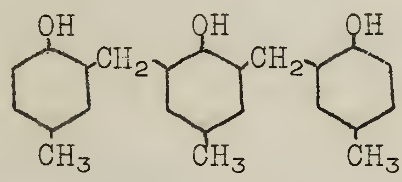


The vinyl theory was discarded because styrene does not polymerize readily under conditions which produce phenol-formaldehyde resins.

In 1912 Raschig suggested a multi-condensation theory similar to the modern conception. His mechanism received little attention.



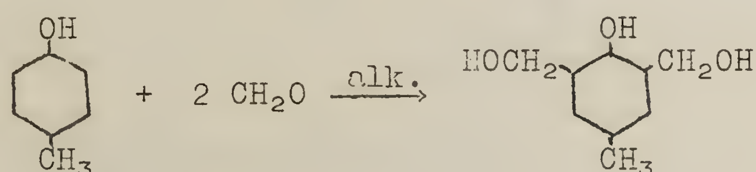
Megson and Drummond found that 2,4'-dihydroxydiphenylmethane is consumed more rapidly than the 4,4' compound and concluded that th polymer has primarily ortho, para linkages. From p-cresol they isolated:

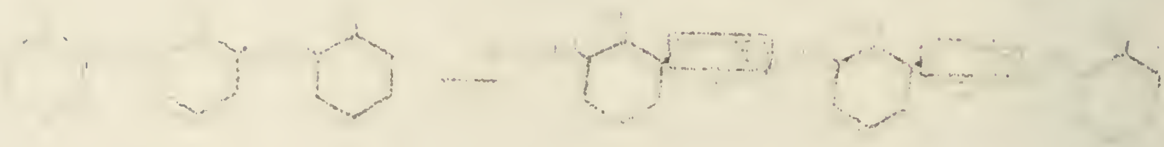


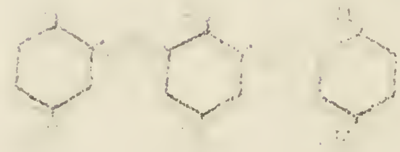
and proved that the phenolic hydroxyls are not involved because it formed only a dibromide. Similar intermediates were isolated from o-cresol. m-Cresol reacts so rapidly that intermediates are difficul to isolate.

Using alkaline catalysts they isolated mono- and polymethylol-phenols. Increase in temperature and concentration decreases the yield of methylol compounds. In alkali insoluble, infusible resins are obtained almost independent of the proportions of phenol and formaldehyde used.

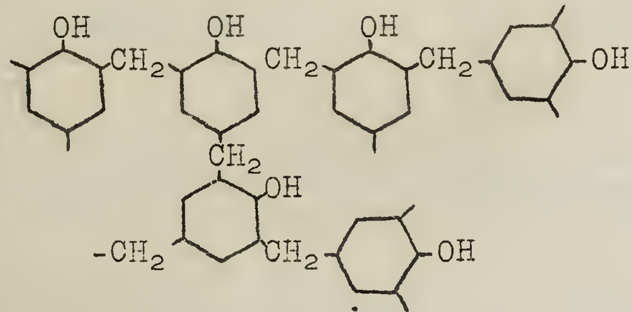
Koebner prepared chains containing from two to seven units by condensing p-cresol with formaldehyde.







These compounds were similar to Novolaks. Phenol and formaldehyde could not be split from them by hydrolysis. They remained fusible and were soluble in common solvents. The sodium salt of the seven-membered compound was insoluble. He could not prepare infusibl resins from p-cresol in which only linear growth is possible. He concluded that Novolaks are di-, tri- and polynuclear linear chains and that resites are due to three dimensional growth of the molecule.



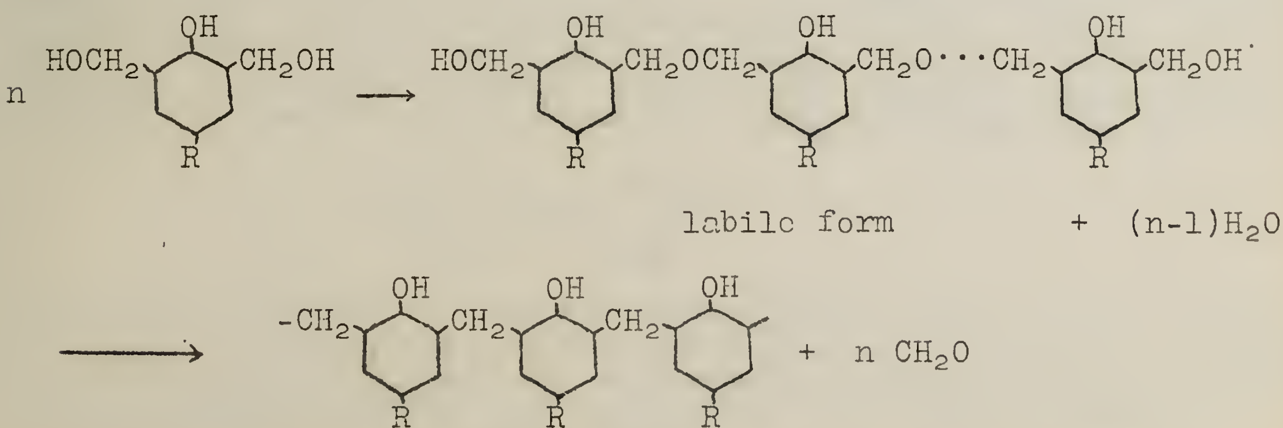
Novolaks which are usually prepared from 0.5 to 1 mole of formaldehyde per mole of phenol have no uncombined methylol groups and hence cannot further condense on heating to form insoluble resit molecules.

Raschig's "multi-condensation" theory is now the accepted mechanism.

Many other phenols and aldehydes have been investigated. Tri-cresol is widely used in making resins. The naphthols are very difficult to resinify. Price is the controling factor in the use of aldehydes, ketones and phenols in commercial resin manufacture.

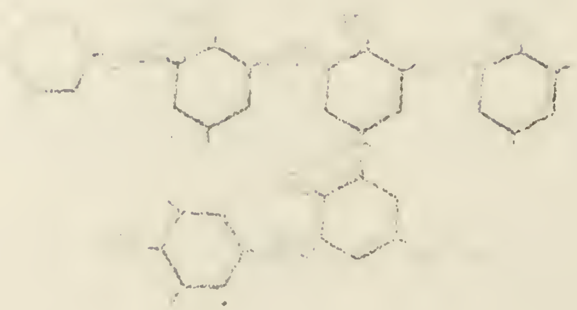
Phenolic Varnish Resins: Polymethylolphenols, or "resols", when heated with basic varnish materials such as resins and drying oils, impart a superior hardness and resistivity to the final film. The exact nature of the reaction is not known.

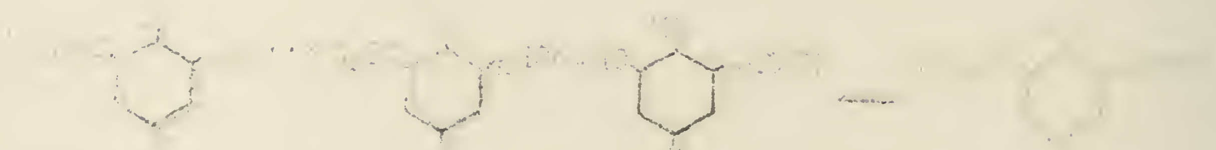
If the dimethylol compound obtained from p-cresol and formaldehyde in strongly alkaline solution is heated gently, only water is split out. Upon further heating up to one mole of formaldehyde can be obtained and a Novolak is the final product. Hönel and Zinke propose the following mechanism.

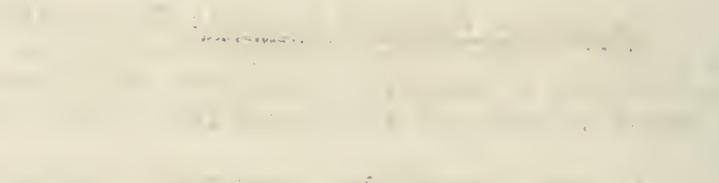


labile form

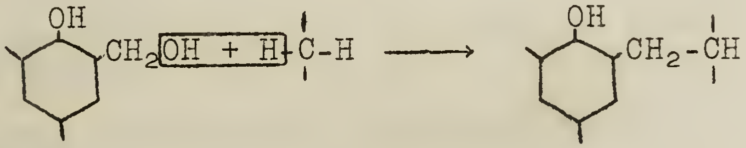
final stable form







When the same resol is heated in a drying oil much less formaldehyde is split out indicating a reaction involving the methylol groups. The labile form shows why low molecular weight resins have the same hardening efficiency. Hönel proposes a condensation with methylene hydrogens or double bond hydrogens.



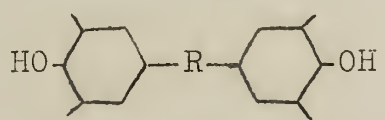
Hilditch and Smith claim it is primarily an addition at unsaturated centers because they could obtain no reaction with paraffin at 240° C. Hönel has since shown that resols will react even with saturated fatty acids at 250° C.

The "heat-hardening" efficiency of a resol is dependent upon the number of methylol groups and the size of the alkyl substituents in the phenol. It increases with the number of methylol groups and also slightly with the size of the substituent. Alkyl groups increase the oil compatibility whereas aryl substituents decrease the oil compatibility. The capacity of a resol to resinify bears no relationship to its oil compatibility. The compatibility of a resol is dependent upon (1) the number of reactive positions, (2) the amount of combined formaldehyde, (3) the size of the alkyl substituents, and (4) the nature of the materials with which it is to be reacted.

The following is a list of basic varnish materials arranged in order of decreasing compatibility. The class numbers indicate the number of alkyl carbon atoms in the meta-position or positions necessary to produce a homogeneous reaction product.

1. Castor oil fatty acids, colophony (abietic acid)
2. Fatty acids of drying oils.
3. Castor oil.
4. Ester gum, cumaron, indene resins, China wood oil, Synourin oil.
5. Linseed oil, perilla oil, soya bean oil, saturated fatty glycerides, waxes, aliphatic unsaturated hydrocarbons.

Thus the trimethylol compound of m-cresol is compatible with class 1 but the corresponding phenol compound is not and at least five aliphatic car on atoms are necessary in the meta-position of a trimethylolphenol to produce homogeneous reaction with class 5. In the type of compound shown below where the dashes indicate either hydrogens or methylol groups at least 10-15 aliphatic carbon atoms per phenolic nucleus are necessary for complete compatibility.



Decreasing the amount of combined formaldehyde increases the compatibility but at the expense of the heat-hardening efficiency. A recent process for using polymethylol compounds in varnishes involves heating it with a higher alcohol. It is believed the etherification of at least one methylol group takes place.

The final polymethylol compound has only two reaction favorable positions available.

Hönel has developed the following rules for compatibility with drying oils:

1. Any resol of the lowest molecular size having but two reaction favorable positions is compatible providing the true resol stage is not exceeded.
2. Resols having more than two reaction favorable positions are generally "thermo-setting" and require a certain minimum number of aliphatic carbon atoms for compatibility.
    a. Three such positions require at least 4-5 aliphatic carbon atoms per phenolic group.
    b. Four such positions demand at least 10 aliphatic carbon atoms per phenolic group providing the resol is in its lowest molecular stage.

Almost any desired properties can be imparted to a varnish if the proper resol and basic varnish material are chosen.

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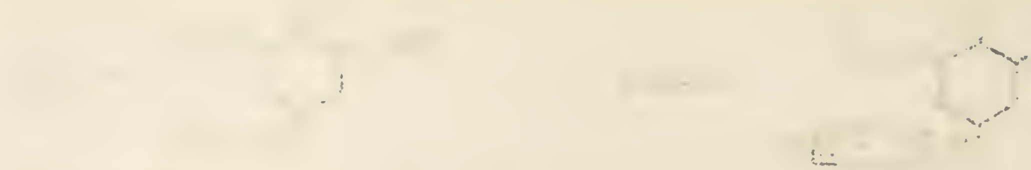
Reported by E. H. Dobratz
March 22, 1939



VITAMIN B_6

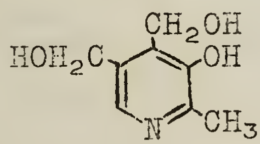
Kuhn -- Kaiser-Wilhelm Institute

The term vitamin B_6 has been given by György to that part of the vitamin B_2-complex which is responsible for the cure of the specific dermatitis developed by young rats fed on a vitamin B-free diet supplemented with purified vitamin B_1 and lactoflavin.

The vitamin is absorbed by fuller's earth from an acidic solution of the alcoholic extract of autolyzed wheat germ. It is eluted with $Ba(OH)_2$ and precipitated by phosphotungstic acid. The compound obtained in this manner is easily dializable, and heat and alkali stable. It has been shown by Kuhn that the vitamin exists in yeast in a high molecular weight, not dializable, heat and light sensitive form. The prosthetic group can be set free from this form by heat, without damage to the vitamin activity.

The vitamin - the low molecular weight compound - is now called "Adermin", a term derived from antidermatitis.

The structure of vitamin B_6 has been shown by Kuhn to be:

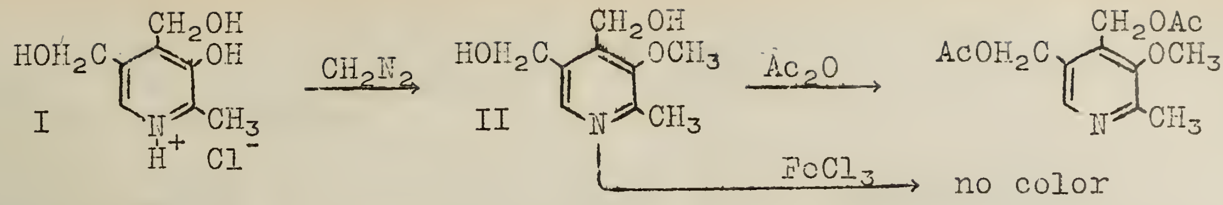


This structure was deduced mainly from the following reactions:

1. Precipitattion with phosphotungstic acid and no loss of activity by treatment with nitrous acid, indicating a tertiary amine.
2. Formation of a monomethyl ether by diazomethane and of a diacetyl methyl ether from the methyl ether.
3. Oxidation of the methyl ether with chromic acid to form acetic acid.
4. Oxidation of the methyl ether with $KMnO_4$ to form a lactone with loss of four hydrogen atoms, and more vigorously to form a tricarboxylic acid from which the anhydride was produced and one molecule of carbon dioxide eliminated.
5. Color reaction of the tricarboxylic acid of the methyl ether indicating an α-carbonyl group, and failure of the dicarboxylic acid to give this reaction.
6. Color reaction and absorption spectra data indicating a β-hydroxypyridine.
7. Partial oxidation of the methyl ether to produce an anhydride-forming methyl-β-methoxypyridinedicarboxylic acid.
8. Synthesis of the acid in 7.

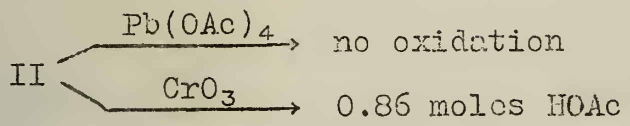
1. György found that adermin is not precipitated by salts of heavy metals but is precipitated by phosphotungstic acid; it is not inactivated by treatment with HNO_2, but is inactivated by treatment with benzoyl chloride. From these observations he concluded the compound does not contain a primary amine group, but is basic and probably contains a hydroxyl group.

2.



These reactions show that adermin contains one phenolic hydroxyl and two alcoholic hydroxyls.

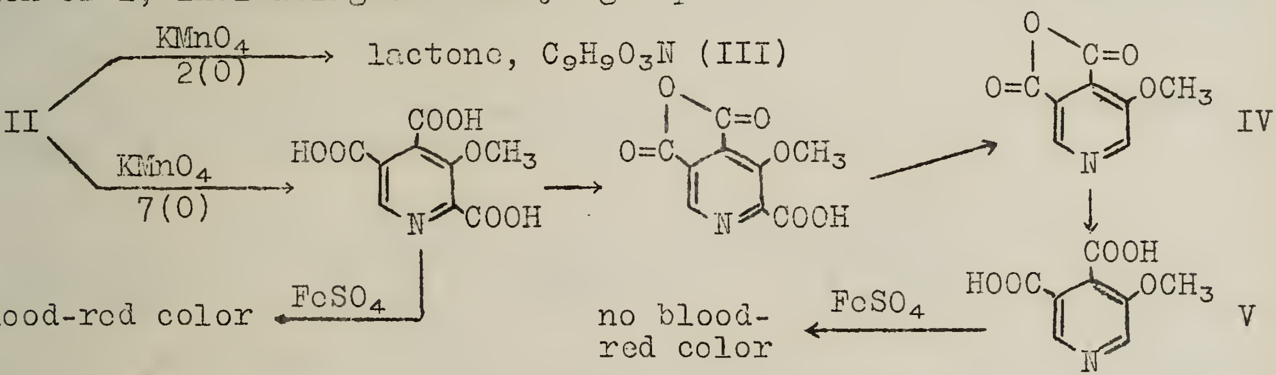
3.



The failure of $Pb(OAc)_4$ to react with II indicates that the compound is not an α-glycol. Criegee has shown that $Pb(OAc)_4$ reacts with a sugar only when $-CH_2OH$ is joined to a carbon atom having a free hydroxyl group.

0.90 moles of acetic acid was obtained by chromic acid oxidation of I, indicating one methyl group.

4.



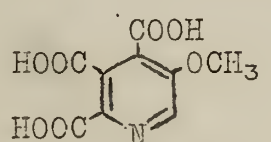
5. A blood-red color with $FeSO_4$ is characteristic for pyridine-α-carboxylic acids. Thus the last carboxyl group was in the α-position.

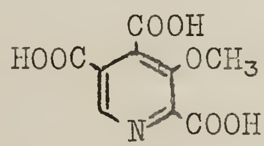
6. The absorption spectra of adermin in HCl and in NaOH are very similar to that of β-hydroxypyridine in the same solutions.

The Folin and Denis phenol reagent gives a deep blue color with adermin. All the β-hydroxypyridines tested with this reagent gave this color, but no α- or γ-hydroxypyridines tested produced such a color.

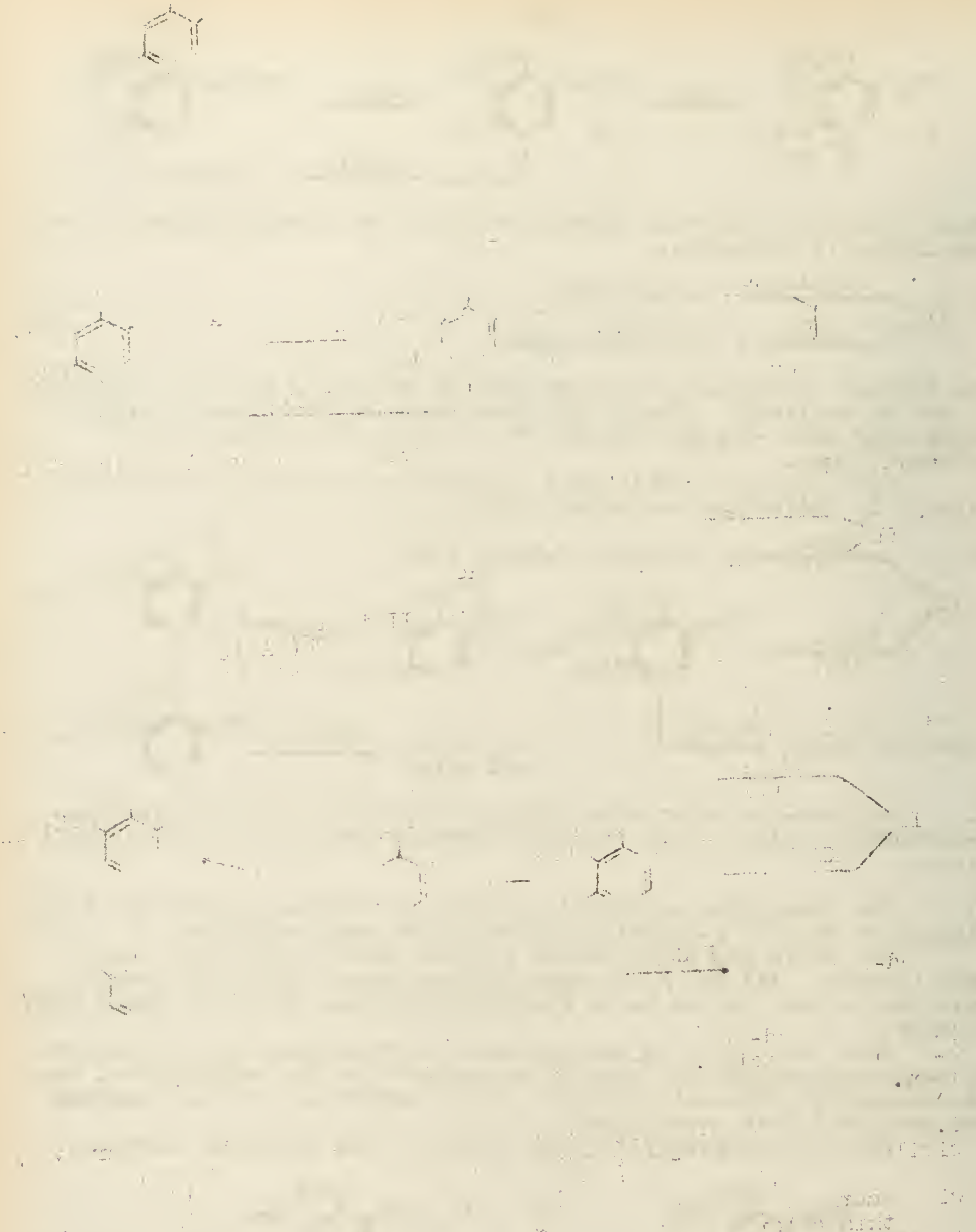
From these data it was concluded that adermin is a derivative of β-hydroxypyridine and that IV is correct for the anhydride of the adermin-methyl ether-dicarboxylic acid. Synthesis of this compound has confirmed this conclusion.

For the tricarboxylic acid there are two possible formulae:

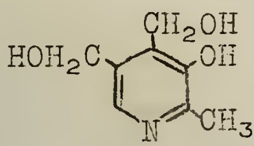
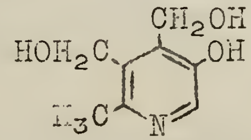
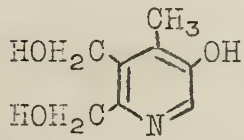
VI 

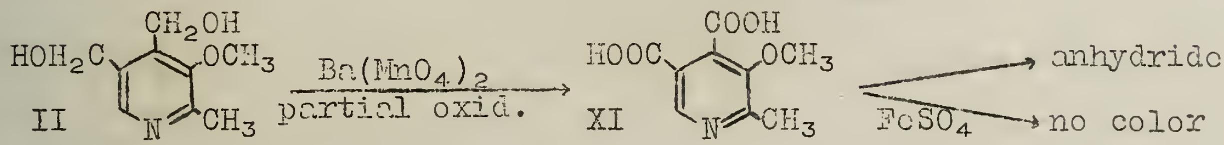
 VII

Since adermin has one phenolic -OH, two alcoholic hydroxyls and one C-methyl and forms a tricarboxylic acid of the methyl ether with loss of six hydrogen atoms and of no carbon, it must be a methyl-di(hydroxymethyl)-3-hydroxypyridine. The lactone formed by mild oxidation with



$KMnO_4$ shows that the two hydroxymethyl groups are on adjacent carbon atoms. From these considerations adermin must have one of the following structures:

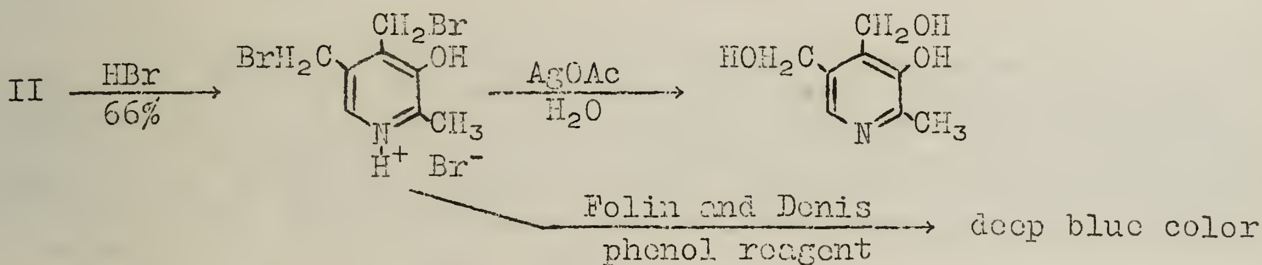
 VIII  IX  X

7. 

The failure of the acid XI to give a color with $FeSO_4$ shows that there is no α-hydroxymethyl group. Adermin cannot be X.

8. 2-Methyl-3-methoxypyridinedicarboxylic acid (4,5) was synthesized and found to be identical with XI formed by partial oxidation of adermin methyl ether.

Kuhn describes the conversion of adermin methyl ether back to adermin by the following reactions:



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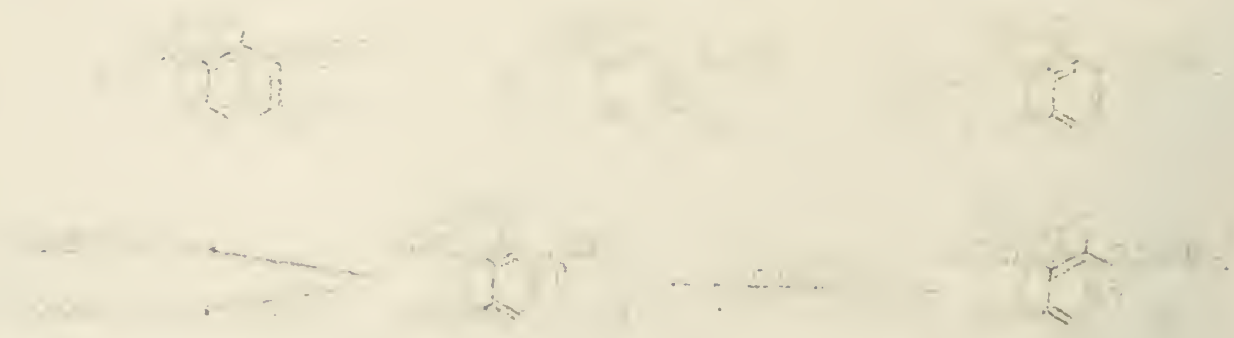
Reported by E. Welch
March 29, 1939



THE RELATIONSHIP BETWEEN FLUORESCENCE

AND CHEMICAL CONSTITUTION

Otto Mumm -- University of Kiel
Henrich -- Erlanger
Fialkovskaja -- State University, Leningrad

The problem of the relationship of chemical constitution and fluorescence has not yet been satisfactorily answered. In fluorescence the process of emission of the absorbed radiation is of very short duration, a time interval of only 10^{-7} to 10^{-9} seconds elapsing between the instant of withdrawal of the exciting radiation and practical cessation of the induced emission. It is in this respect that it differs from phosphorescence in which the process of emission is extended over an easily measured period of time.

In the case of fluorescence, the mechanism involves first the primary process of absorption in which an atom is raised to an excited state. This is then followed by a reëmission of the absorbed radiation in either a single step where the emitted quantum has the same energy as that of the exciting ray (resonance), or in a stepwise fashion, giving off radiation of longer wave length and possibly involving dissipation of some of the energy by inelastic collisions with other molecules.

It is Waters' contention that fluorescence emission is necessarily concerned with the reformation of stable valency bonds (or possible stable "lone pairs" of electrons) from previously activated molecules. In support of this he offers that when two halogen atoms combine, the resulting molecule is so stable that energy is emitted as fluorescence under favorable pressure and temperature conditions. For example: $2\,I \longrightarrow I_2 + h\nu$.

It might seem reasonable to suppose that this light energy emission might be associated with the chemical action of recombination of the neutral free atoms to diatomic molecules. This might be extended to other cases of fluorescence which might be concerned with the dissociation of a covalent bond into free radicals, followed by a recombination of these radicals once more. The emission of fluorescence might then indicate that the dissociation of a covalent bond in a molecule had previously occurred.

Among some of the considerations which he offered in support of this suggestion are the following:

1. Fluorescence of Na and Hg vapors is definitely associated with neutral diatomic molecules Na_2 and Hg_2. These can be produced only by association of single atoms.

2. Fluorescent inorganic molecules can dissociate into free radicals such as NO.

3. The inhibition of fluorescence by added substances can only be brought about by those compounds which can easily lose an electron (ex. iodide ion or O_2). These same substances can also inhibit photochemical reactions by terminating chain processes and combine instantly with known free radicals.

4. Only certain classes of organic molecules possessing unsaturated conjugated structures are fluorescent and all these compounds

[illegible]

[illegible]

[illegible]

[illegible]

In the case of [illegible]

[illegible]

[illegible]

[illegible]

1. [illegible]

2. [illegible]

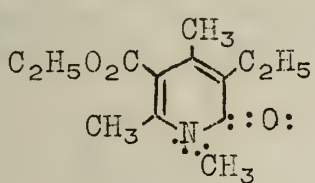
3. [illegible]

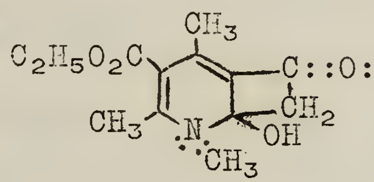
4. [illegible]

are capable of yielding free radicals, either by dissociation or addition of alkali metals.

5. All aromatic compounds, even if not otherwise fluorescent, give characteristic "Tesla" spectra, the seat of which is the aromatic ring and which it has been suggested is associated with tautomerism of valency bonds between two special Kekule "phases". Any such isomerism, however depicted, must involve fission of valency bonds with subsequent reunion of momentarily existing free radicals.

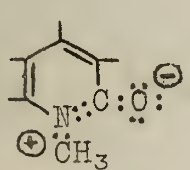
Mumm and his coworkers have spent many years working with compounds in the pyridine series and found that a great number of these compounds had fluorescent properties. From this he has formulated an opinion as to the characteristic structure necessary to produce fluorescence. As a general example we will consider first 1,4,6-trimethyl-3-ethyl-5-carbethoxypyridon (I) and all other products with different substituents in positions 3, 4 and 5. These completely substituted pyridones are used in order to show that a possible enolization of the N hydrogen to the carbonyl oxygen is not necessary in the mechanism. All of these pyridones show strong fluorescence even in the solid state, when activated by ultra-violet light.

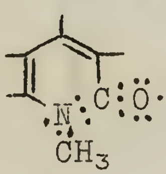
I 

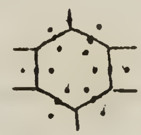
 II

However, as soon as the structure changes from the characteristic pyridon grouping, the fluorescence disappears as well. This is also true of compounds having a structure as in II which do not show a trace of fluorescence. Thus he claims that only those compounds having the grouping -N(CH_3)-CO- can be responsible for fluorescence.

Since the possibility of enolization has been removed by substituting a methyl for the N hydrogen, that need not be considered. However, the possibility of a shift to a betaine structure (III) has not been eliminated and according to von Auwers the spectrochemical data on the N-alkyl pyridones indicates that the structure is somewhere between the carbonyl and the betaine formulae. This is explained by a partial neutralization of the residual affinity between the doubly bonded oxygen and the nitrogen. In other words we have here a case of mesomerism and I and III are only limiting formulae. Thus

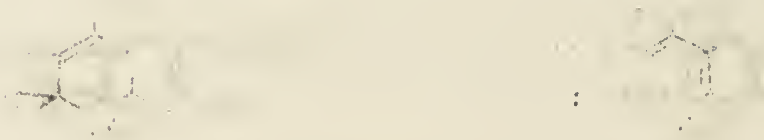
III 

IV 

V 

for the intermediate state we can write the structure as in IV (a difree radical) which is comparable to the time average formula of benzene (V) as advocated by many of the modern theorists.

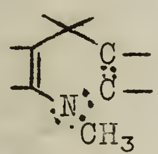
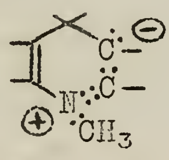
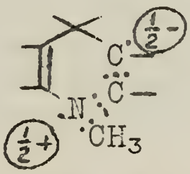
When such a molecule absorbs light, the quantum which is of low energy raises the electron which is least firmly held in its normal level, to an excited state. Thus one of the electrons shown between C and N or C and O in IV would be of this type. This action then disturbs the valence forces in the molecule and upsets the reso-



nance of the molecule. For example, if one of the electrons in IV between C and N is excited, then the free electron on the nitrogen will be drawn in closer to the triad grouping and upon emission the excited electron drops down to form the normal double bond between N and C as in III. A similar process takes place if an electron is disturbed between C and O in IV but in this case it drops back to form the normal double bond as in I.

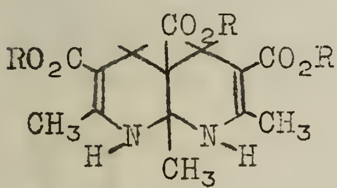
Other substances of the pyridine series which Mumm studied were the γ- and α-dihydropyridines. In this case the γ-dihydro compounds are white, fluoresce strongly and exhibit no basic character, whereas the α-dihydro compounds are mostly weakly basic, yellow in color and exhibit no fluorescence.

If one considers the N-methylated γ-dihydropyridines there is a marked similarity in molecular structure to the α-pyridones. Thus in VI we have the formula as normally written and its tautomer in VII. Correspondingly the intermediate state can be written as analogous to that of the pyridones (VIII) and is again a di-free radical with a half positive charge on the nitrogen and a half negative charge on the β-carbon. The same would then hold true as to light absorption and emission as in the case of the pyridones.

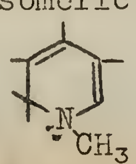
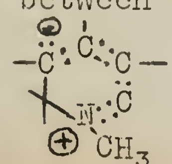
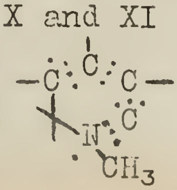
VI  VII  VIII 

As support for the assumption of VIII is introduced the fact of the lack of basic character of the γ-dihydropyridines. Thus, although VI indicates the presence of a free electron pair which is normally easily capable of bonding with a hydrogen ion, it cannot do so in this case.

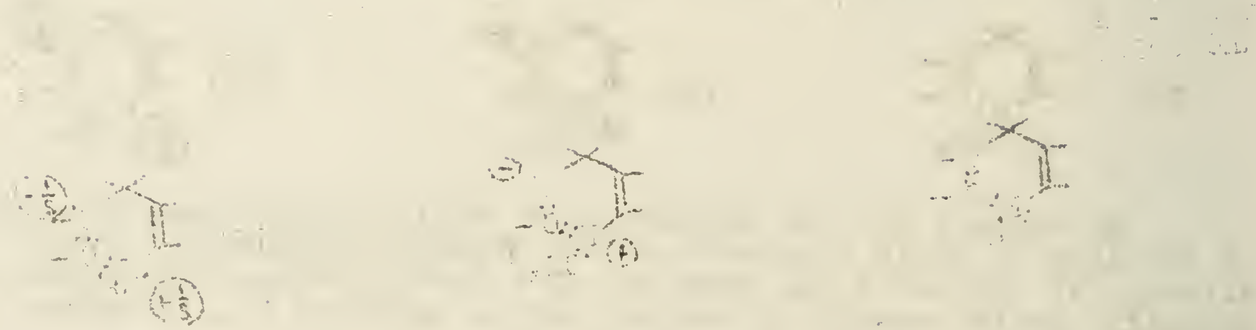
There may be the objection that in this case the molecule is symmetrical, making carbon atoms 2 and 6 equal and that the source of fluorescence is due to a combined interaction of the two double bonds. However, this can be met with the fact that a substance having a structure as in IX with only one double bond can be prepared and that these substances fluoresce as deeply blue as the γ-dihydropyridines and in which the basic character is also lacking.

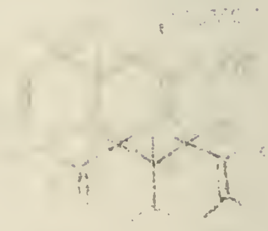
 IX

Now if the α-dihydropyridine is considered in the same light as the α-pyridones and the γ-dihydropyridines it is readily seen that here the resonance must go through a greater part of the molecule, namely up to carbon 5. Accordingly the negative charge is carried further so that the mesomeric intermediate between the limiting forms X and XI is XII.

X  XI  XII 

As a consequence of the greater distance over which the





resonance energy must be distributed the electrons in the mesomeric form (XII) are more loosely bound. Accordingly the bond between the nitrogen and the α-carbon is also decreased in energy and one of the electrons can be more easily diverted to furnish a lone electron pair on the nitrogen. This then accounts for the more basic character of the α-dihydro over the γ-dihydropyridine. On account of this greatly loosened bonding of the electrons in XII there is also a lessened expenditure of energy necessary to raise them from their normal level. Thus for this purpose light of longer wave length is needed. This all correponds to the fact that the α-dihydro compounds absorb in the blue and are thus colored yellow, whereas the γ-dihydro compounds absorb in the ultra-violet and are white.

A further consequence of this is that upon falling back to its normal level, the electron in the α-dihydro compound emits rays of longer wave length which in general are no longer visible. Therefore the α-dihydrocompounds do not fluoresce but when in exceptional cases fluorescence does appear, the emitted light instead of being blue, as in those compounds mentioned earlier, is green or of longer wave length.

It appears then that the connection between color and chemical constitution is almost of the same nature as the forementioned connection between fluorescence and constitution. The essential difference lies in the fact that the emission of radiation following upon the dropping of an excited electron consists of rays of greater wave length which no longer belong to the visible part of the spectrum.

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Reported by M. H. Gold
March 29, 1939

ORGANIC COMPOUNDS CONTAINING N^{15}

Schoenheimer -- Columbia University

Since the discovery of isotopes and of improved methods for their concentration, attention has been turned towards their use as indicators in following reactions. Radioactive isotopes have been used extensively in inorganic chemistry, but as yet have not proved to be of value in organic chemistry, since radioactive isotopes of organic elements of long half life have not been prepared. Stable isotopes have to be used; these have the disadvantage that their concentration is more difficult to determine.

Schoenheimer has conceived the idea of using N^{15} and D to follow the metabolism of proteins. It has been found convenient to use a mass spectrometer for determination of N^{15}. With this apparatus, only very small amounts of gas are necessary, and a high degree of accuracy can be obtained. By analysis of atmospheric nitrogen and of various compounds, the normal N^{15} content was shown to be 0.368 atom per cent. Several naturally occurring amino acids were also investigated. These had values ranging from 0.000 to 0.010 atom per cent excess N^{15}. The higher values probably result from some sort of a minute fractionation process.

In carrying out a mass spectrometer analysis, the following technique was used:

1. Determination of total N, and simultaneous conversion into NH_4^+ by the Kjeldahl method.
2. Conversion of NH_4^+ into N_2 by alkaline hypobromite:

$$2\ NH_4^+ + 2\ OH^- + 3\ NaOBr \longrightarrow N_2 + 3\ NaBr + 5\ H_2O$$

3. Admission of gas to spectrometer.
4. Actual measurement.

In order that the data would be significant, Schoenheimer demonstrated that the C-N bond is rather stable and would not undergo exchange reactions. No exchange of N was noticed in any of the following systems: N - NH_3 or amino acids; NH_3 - amino acid; amino acid - amino acid; hippuric acid - amino acid; urea - amino acid. All these were carried out at 37°. Some evidence of an exchange reaction between urea and NH_4Cl was observed at 100°, probably because of the equilibrium $NH_2CONH_2 \rightleftharpoons NH_4^+ + CNO^-$.

The amino acids were prepared according to Knoop and Oesterlin method and by the Gabriel synthesis. The first method involves the hydrogenation of an α-keto acid in the presence of ammonia:

$$RCOCOOH + NH_3 + H_2 \xrightarrow{Pd} \underset{NH_2}{RCHCOOH} + H_2O$$

For monocarboxylic acids, two mols of ammonia were necessary; for dicarboxylic acids, three. Norleucine, phenylalanine, tyrosine, glutamic acid, aspartic acid, and alanine were prepared in this way. Gabriel's synthesis was applied in the synthesis of deuteroleucine and lysine.

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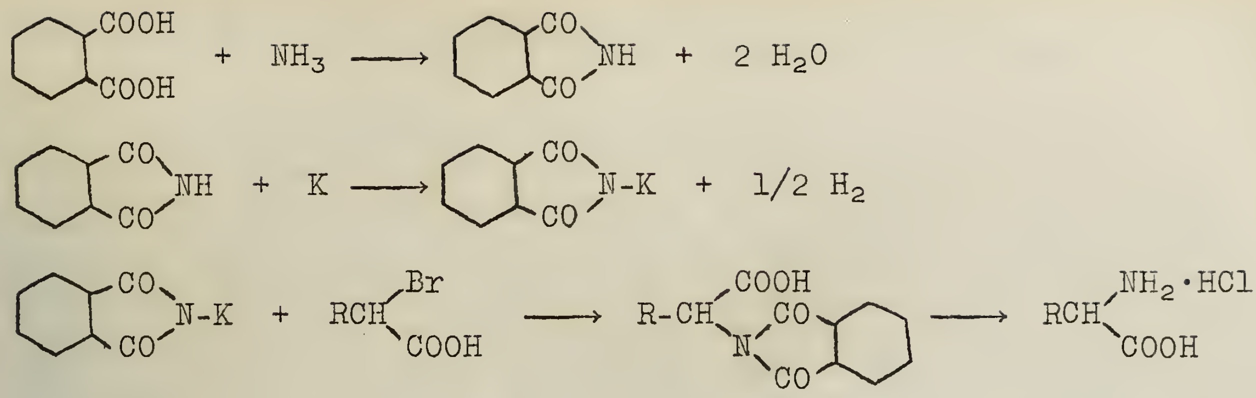

An example of the use of N'5 is Schoenheimer's work on hippuric acid. It is a well known fact that large quantities of benzoic acid in the organism are detoxified by glycine to give hippuric acid.

$$C_6H_5COOH + NH_2CH_2COOH \longrightarrow C_6H_5CONHCH_2COOH$$

Glycine N'5 was administered with benzoic acid, but even when there was an excess present, only 1/4-1/3 of the N'5 appeared in the urine as hippuric acid N'5. Much of the glycine used in detoxification was therefore supplied by the tissues.

The methods used by Schoenheimer appear to constitute a valuable tool not only for biochemists but also for organic chemists in following the course of reactions.

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Reported by L. C. Behr
April 5, 1939

NATURAL AZULENES

Pfau and Plattner -- Laboratory of Firm L. Givaudan and Co., S.A.

The first recorded observation of a deep-blue compound occurring in a natural oil was made in the 15th century. Since that time it has been shown that many ethereal oils contain these blue compounds, or the latter may be obtained from them by chemical transformations. Due to their distinctive deep-blue or azure color Oessi named them "azulenes" in 1863. In all there are over 260 described ethereal oils which contain azulenes or azulene-like compounds, and which correspond to about 20% of the known oils. The sources which have been most thoroughly investigated are camomile. elemi, eucalyptus vetiver, guaiacol, gurjun, and milfoil oils as well as brown-coal-tar neutral oils, certain fungi, and a synthetic tarry material called cuprene-tar obtained by passing acetylene over metallic copper.

In general the azulenes are obtained from the sesquiterpene and sesquiterpene-alcohol fractions of ethereal oils by dehydrogenation with S, Se, or catalytic Ni. They are separated from other products by their solubility in concentrated mineral acids (50% H_2SO_4 or 80% H_3PO_4) and recovered by subsequent dilution of the acid solutions. Picrates, styphnates, trinitrobenzenates, trotylates, and $H_4Fe(CN)_6$ addition compounds may be prepared easily, and these can be decomposed by $(NH_4)_2S$, NH_3, or chromatographic absorption on activated alumina to give the pure azulenes.

The name "azulenes" has been used for the entire class of compounds in the same manner that "naphthalenes" implies all compounds which have a naphthalene nucleus but various aliphatic side chains. In a more strict sense the name "azulene" refers to the basic compound of the group with a formula of $C_{10}H_8$ (IX), isomeric with naphthalene.

All azulenes have a naphthalene-like odor, and range in color from deep blue to violet. They react readily with Br_2, NOCl, and N_2O_3, but the products are too unstable for recrystallization. Metallic sodium decolorizes an ether solution of an azulene, and a brown crust is formed on the sodium. By addition of moist ether the azulene may be regenerated. The anti-inflammatory action of the ethereal oil of camomile as tested by mustard oil irritation to rabbit eye, and irradiation erythema in human beings, rats, and pigs has been attributed to one constituent, azulene.

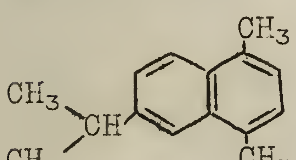
Various investigators have checked the molecular weight and degree of unsaturation of these natural azulenes and have found that they all possess the formula of $C_{15}H_{18}$ and will take up five molecules of H_2, being transformed to colorless saturated hydrocarbons. Each investigator who isolated an azulene from a different ethereal oil gave a characteristic name to the azulene; for example, that from camomile oil was called chamazulene, that from eucalyptus oil was called eucazulene, and that from elemi oil was called elemazulene. Such was the state of confusion of the literature when Pfau and Plattner took up the study. They found that treated guaiacol, after dehydrogenation by S or Se, gave two different azulenes which they termed S-guaiazulene and Se-guaiazulene. After obtaining these in the pure state, preparing derivatives, and studying their absorption spectra, they proceeded to compare the other known azulenes with these tw

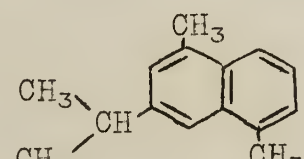
To their surprise they found that all of the azulenes which they prepared from the other natural oils by dehydrogenation were identical with S-guaiazulene with the exception of an azulene which was obtained from vetiver oil by dehydrogenation with Se. This, then, simplified the study by limiting the number of natural azulenes principally to three: vetivazulene, S-guaiazulene, and Se-guaiazulene.

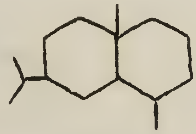
In order to prove the structures of these azulenes oxidation and ozonization studies were carried out. These yielded such a variety of compounds that Pfau and Plattner decided little progress could be made in that way. Similar studies were carried out by Kremers who suggested two possible structures both of the benzofulvene type, based upon the fact that the azulenes were bicyclic, colored, and formed dimers by the addition of sodium. The ideas of the benzofulvene and naphthalene nucleus were completely rejected by Pfau because these compounds do not form addition compounds with $H_4Fe(CN)_6$ while all azulenes do, and also because of some dehydrogenation studies to be discussed later. In 1926 Ruzicka and Rudolph expressed the general facts known concerning the structure of the azulenes by stating: "The color of the azulenes is due to an especial, up-to-now unknown type of grouping of five double bonds (without an aromatic ring) in a bicyclic ring of carbon atoms, which is very similar in constitution to the sesquiterpene compounds if not identical with them."

Following the same procedure of Mayer and Shiffner, who found that certain alkyl groups migrated from the α- to β-position on a naphthalene ring when these α-alkylnaphthalenes were passed over silica gel, Pfau and Plattner carried out a similar reaction with S-guaiazulene. Good yields of naphthalene hydrocarbons were obtained but in mixtures which indicated a shift in alkyl groups. Hence no further work was done on this reaction.

By dehydrogenation of treated guaiacol with P and HI there was obtained, after separation of azulenes, a naphthalene hydrocarbon of the formula $C_{15}H_{18}$ (therefore an isomer of cadaline and the azulenes) Another isomeric hydrocarbon from the vetivazulene-yielding fraction of vetiver oil was obtained in a like manner. The former by picrate and trinitrobenzenate was shown to be 1,4-dimethyl-6-isopropylnaphthalene (I) while the latter was 1,5-dimethyl-7-isopropylnaphthalene (II Both had been previously synthesized and identified by Ruzicka.


I


II

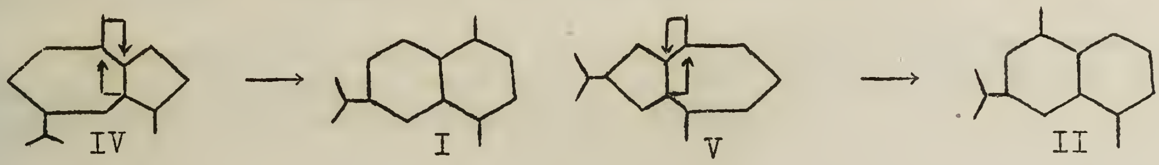

III
(eudesmene skeleton)

From such results Treibs postulated that III was the probable azulene skeleton, but Pfau disproved this by dehydrogenating a saturated eudesmene-type compound to get no azulene while decahydroguaiazulene could be transformed back into an azulene. It was therefore concluded by Pfau that the naphthalene skeleton was formed from some other ring system. Splitting the ring from a sesquiterpene compound by mild oxidation followed by ring closure led to a cyclic



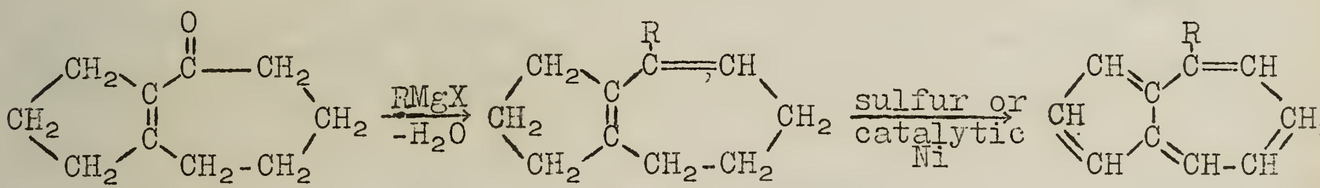
ketone which had one fewer carbon atoms in the ring. This ketone by dehydrogenation led to a phenol, which made the original terpene structure seem to have a seven-membered ring.

Connecting these results then the formula of naphthalene derivatives could be explained; the rearrangement could be considered analogous to the retropinacolone rearrangement:



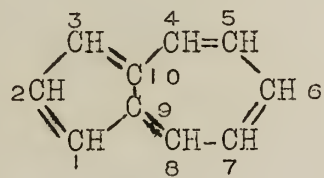
IV I V II

In order to substantiate these findings several compounds of the bicyclo-(0,3,5)-decane system were synthesized. Hückel and coworkers had previously prepared cyclopenteno-cycloheptanone (VI) in order to show that both cis and trans forms were strainless. By addition of a Grignard reagent and subsequent dehydration and dehydrogenation azulenes were obtained according to the following scheme:



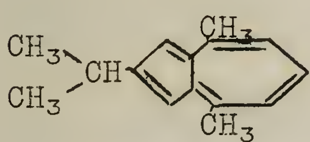
VI VI

R = CH_3
R = C_2H_5
R = C_6H_5

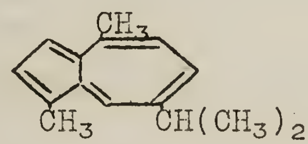


IX

Mixtures were obtained in the case of VIII but the true azulenes were separated by concentrated H_3PO_4. Yields were low due to the sensitivity toward acids. Compounds represented by VIII were blue in color, had very similar absorption spectra, and all derivatives were much like those of natural azulenes. These findings confirm that the azulene-type is of a new kind of ring system which has a five and seven-membered ring fused through adjacent carbon atoms. Thus vetivazulene would be 2-isopropyl-4,8-dimethylazulene (X), while S-guaiazulene would have the constitution of 1,4-dimethyl-7-isopropyl azulene (XI):

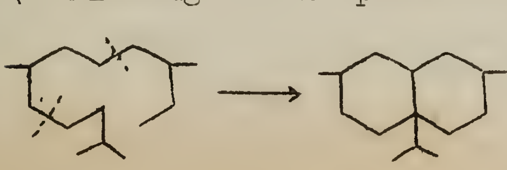


X

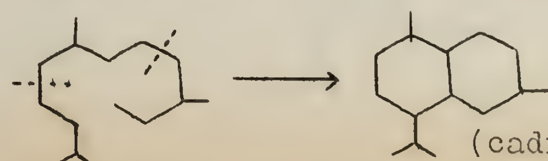


XI

As a final discussion, of the types of bicyclic sesquiterpenes and their derivatives the largest number belong to the group of hydrogenated naphthalene derivatives, bicyclo-(0,4,4)-decane, and may be traced back to three types by cyclization of three isoprene units (following the isoprene rule):

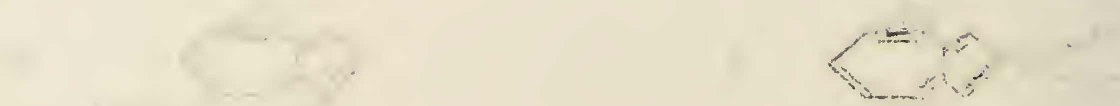


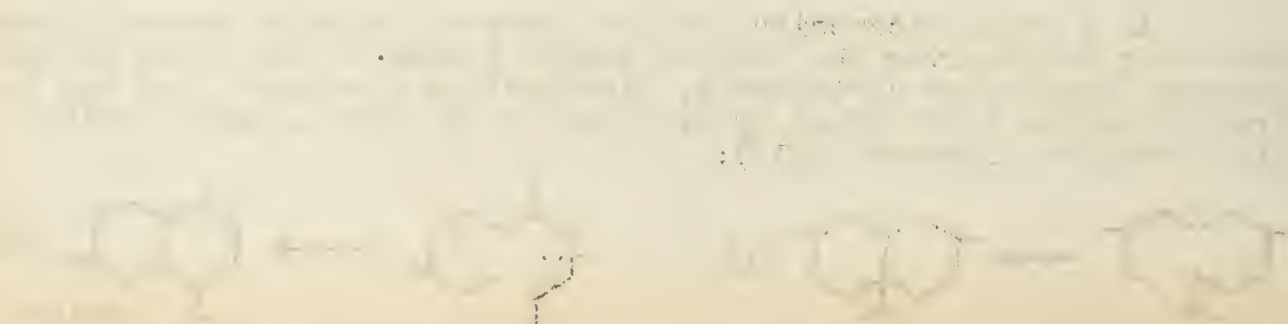
XII

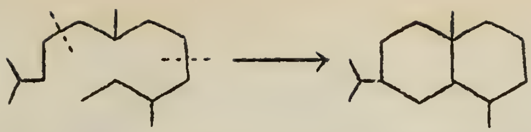


XIII

(cadinene t...)



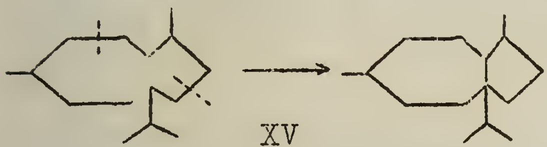




XIV
(eudesmene-type)

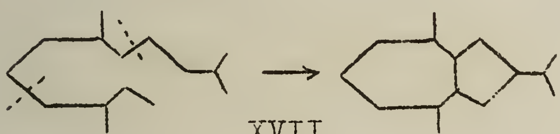
The first type (XII), originally proposed by Wallach, has not been found in nature. Types XIII and XIV are well-known.

The analogous structure of bicyclo-(0,3,5)-decane leads to nine possible skeletons (whereby it is not to be implied that all of these possibilities are realized in nature):

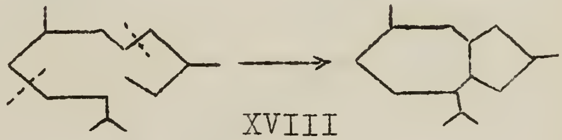


XV

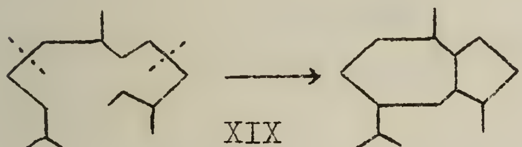
XVI



XVII

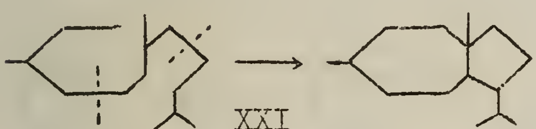


XVIII



XIX

XX



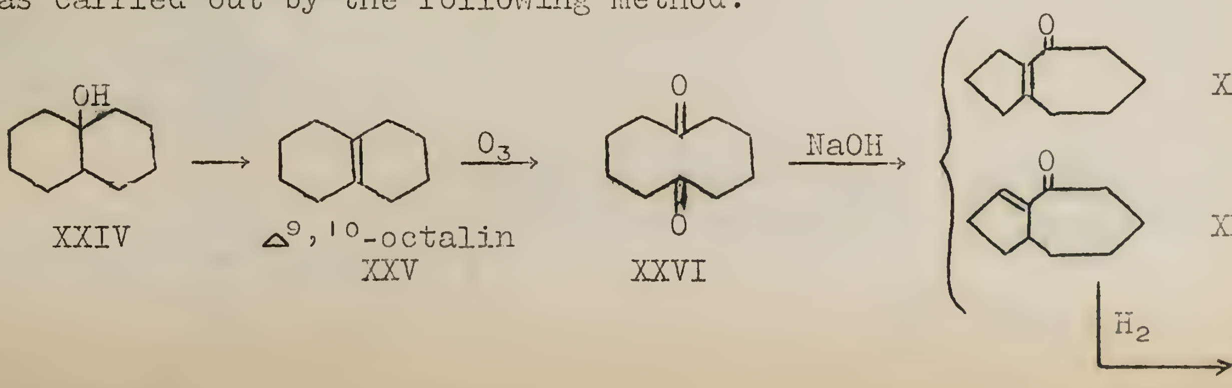
XXI

XXII

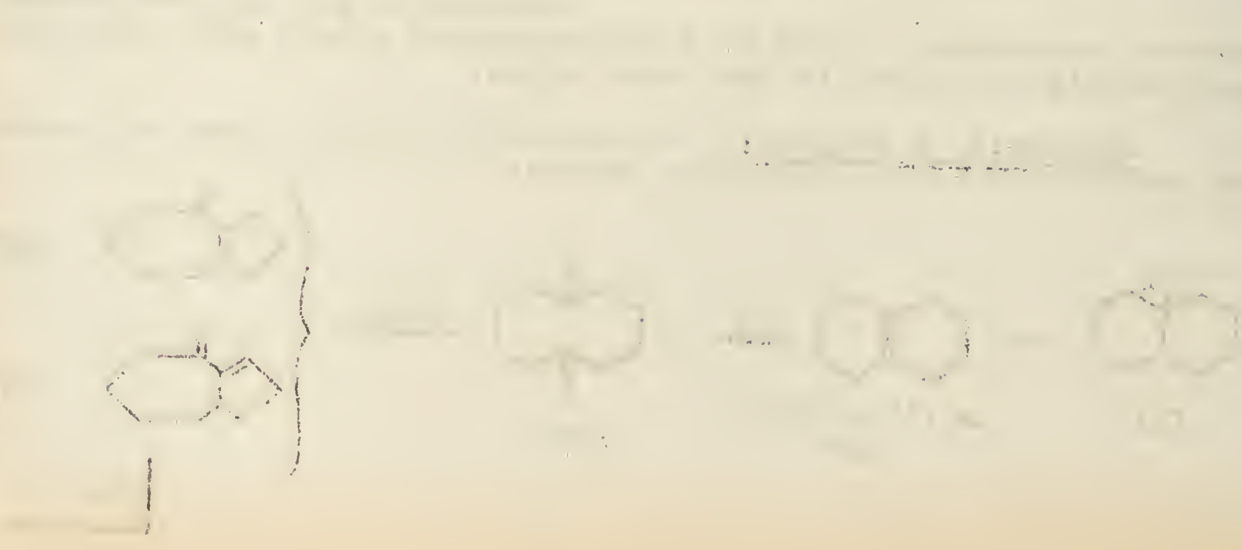
XXIII

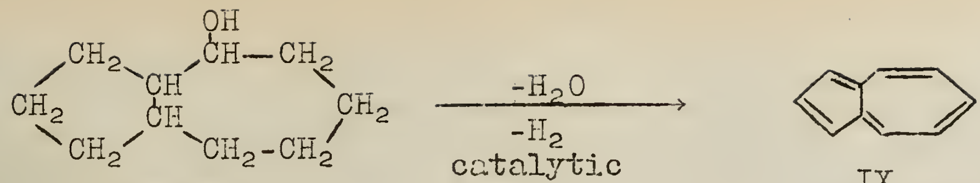
Type XVII is known with certainty to be that of vetivazulene, while very probably type XIX represents S-guaiazulene. The further work concerning natural azulenes and numerous as yet unknown sesquiterpene derivatives, which by dehydrogenation should give azulenes, can probably be traced to the other types.

Synthesis of Azulene: The synthesis of the parent hydrocarbon was carried out by the following method:



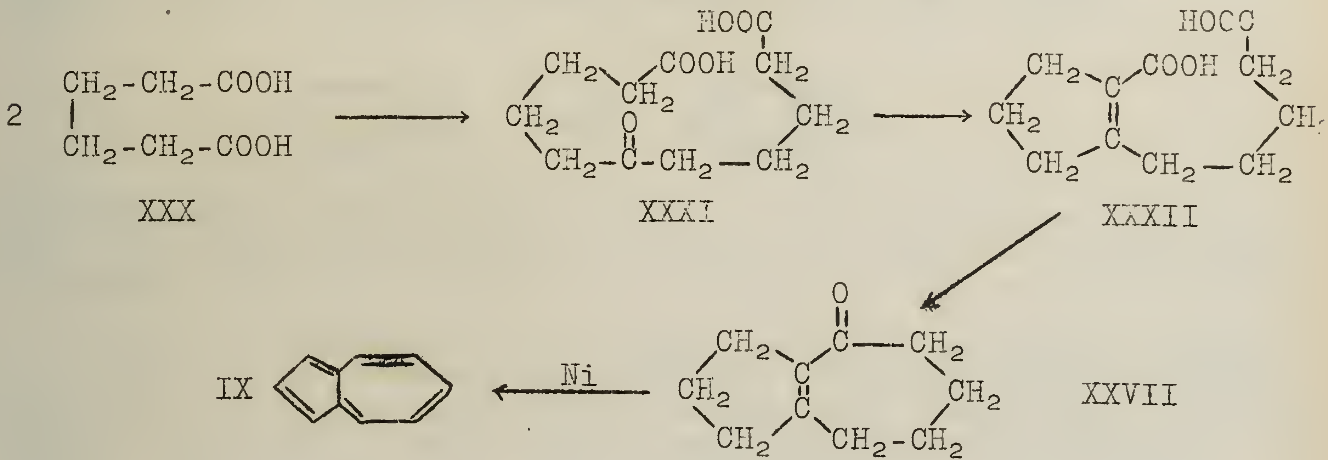
XXIV $\Delta^{9,10}$-octalin XXV XXVI XXVII XXVI





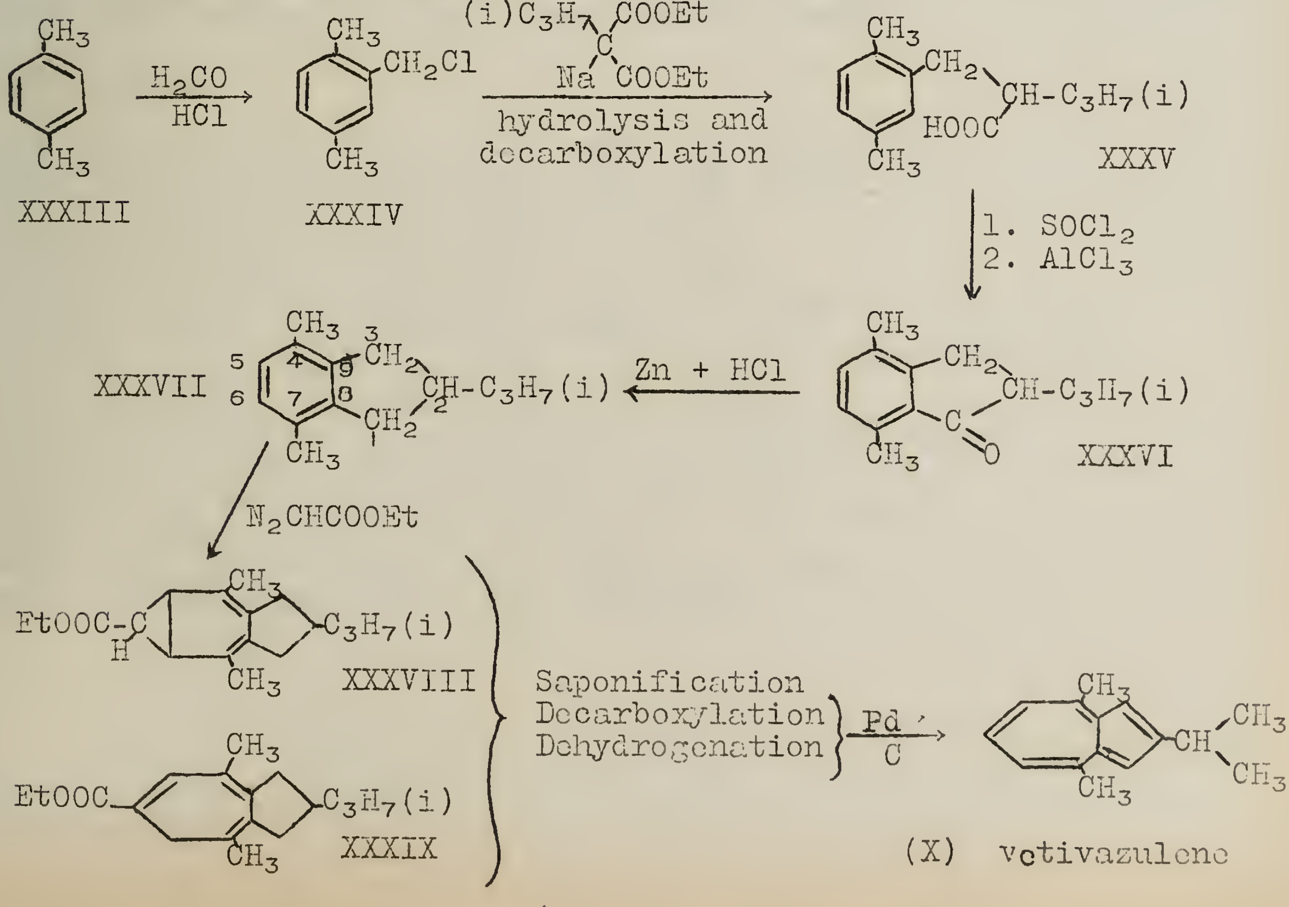
XXIX IX

This synthesis also cleared up the question as to the nature of the blue compound obtained by Hentzchel and Wislicenus in 1893 by dry distilling the calcium salt of adipic acid. Pfau repeated their work using catalytic Ni, isolated and identified the blue compound as azulene itself. He gives the following mechanism for the reaction:



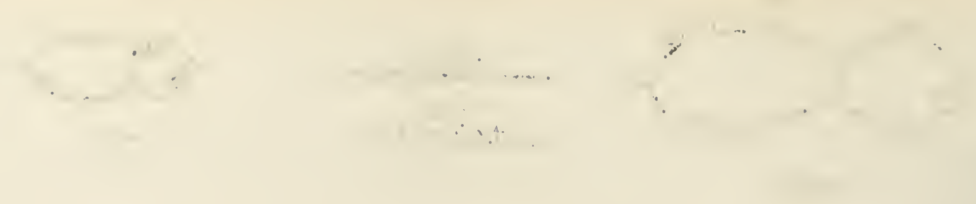
XXX XXXI XXXII XXVII

Synthesis of Vetivazulene:



XXXIII XXXIV XXXV XXXVI XXXVII XXXVIII XXXIX

(X) vetivazulene



Compound XXXVII is here formulated with the arrangement of double bonds which are necessary, according to Mills and Nixon and also Fieser and Lothrop, for hydrindene derivatives. Addition of the diazoacetic ester to any of the three positions 4-5, 5-6, 6-7 would lead to the same end product; 4-9 and 7-8 addition would be sterically difficult, while 8-9 addition seems impossible. The vetivazulene thus prepared was identical in all derivatives and also in absorption spectra with that from the natural source. This, then, is the first complete synthesis of a "natural" azulene.

In closing it should be pointed out that different forms of unsymmetrically substituted azulenes may exist, as follows:

The relationship here is quite similar to that of aromatic hydrocarbons. An exhaustive discussion of this is to occur in a later paper by Plattner and Pfau.

Recently Sklar made a systematic study of chromophore groups in relation to their absorption spectra. He worked out a method of calculating the absorption bands of compounds by calculating resonance levels. The equations used contain only one parameter which is entirely dependent upon the heat of hydrogenation of the compound. He has successfully applied this to azulene and has been able, without the use of any optical data, to determine values for its absorption bands which agree well with experimental results.

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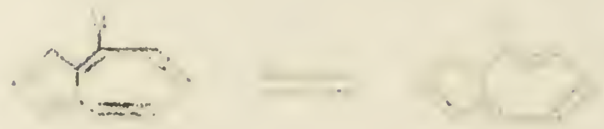
Reported by J. J. Denton
April 5, 1939



STERIC HINDRANCE IN SUBSTITUTED BENZALDEHYDES

The term, steric hindrance, is applied to the effect produced by groups in a molecule, which, although they do not enter into the reactions, exert a profound influence on the speed or course of the reaction taken by the functional group. The reaction which takes place then becomes the resultant of the reactivity of the functional group and the steric hindrance provided by the radical or radicals which it holds.

Although very little is known about the actual cause of these deviations from normal reaction course, there emerges from a large number of studies one very significant if not entirely general rule. That is, that these effects are associated primarily with reactions which are formulated as being additive rather than metathetical.

This paper presents the results of a number of investigators who have studied some common reactions of variously substituted benzaldehyde derivatives in order to observe the influence of these substituents.

Acetal Formation: The well known experiments of Victor Meyer have shown that esterification of aromatic acids is inhibited when the two ortho hydrogen atoms are replaced by alkyl, Cl, Br, I, or NO_2 groups and, conversely, that the esters of such di-orthosubstituted acids are especially difficult to saponify. Since the conversion of aldehydes to acetals is a process entirely similar to esterification, Fischer and Giebe[1] studied the ease of dimethyl acetal formation of the aldehydes corresponding to the acids used by Meyer. They discovered entirely different effects. o-Nitrobenzaldehyde reacts easier than benzaldehyde as is the case with 2,5-dichloro- and 2-nitro-3,6-dichlorobenzaldehyde. In these cases the electronegative substituents have exerted an accelerating effect in spite of their ortho position and high molecular weight. The same authors tried 2,4,6-trimethylbenzaldehyde. In this case the reaction was more difficult than with benzaldehyde but the difference is not very great since, under the same conditions, benzaldehyde gave 52% of the acetal while the mesityl aldehyde gave 32%. The general conclusions reached by these investigators was that substituents in the ortho position induce no great hindrance to acetal formation.

Similar conclusions were reached by Lock[2] after studying 2,6-dichloro- and pentachlorobenzaldehydes. The 2,6-dichlorobenzaldehyde reacted somewhat slower than benzaldehyde but the yield could easily be increased by prolonging the reaction time. The following results were reported:

Compound	Time in hrs.	% yield of acetal
benzaldehyde	24; 60	43; 50
pentachlorobenzaldehyde	96	60
2,6-dichlorobenzaldehyde	24; 96	13.6; 43

The only example which indicates a definite hindrance is that of 2,4,6-trinitrobenzaldehyde reported by Bamberger and Elger[3]. They were able to get no acetal formation by ordinary methods but did obtain a slight yield after very long standing.

Perkin Reaction: Studies on the Perkin reaction with substituted benzaldehyde have led to some interesting results. The original investigations by Meyer and Beer[4], whose results are shown in the following table, indicate that, in general, mono-orthosubstituted benzaldehydes react more readily than benzaldehyde itself.

Substituent in ortho position	H	NO_2	Cl	I
Yield of corresponding cinnamic acid	48	51	66	85.5

Similar studies on variously substituted derivatives by Reich, Salzman and Kawa[5] and by Lock[2,6,7] indicate that no hindrance is observed except in the case of methyl derivatives. The combined results of these investigators are given in the following tables.

Position of Cl atoms	2	3	4	2,5	2,6	2,3,6	2,3,4,5,6	H
Yield	71	63	52	78	82	66	25-30	45

In general, all chloro derivatives gave higher yields than benzaldehyde itself. The highest yields were obtained from the ortho- and diortho-substituted derivatives. The low yields of the pentachloro derivative is attributed to its great insolubility rather than to steric hindrance (Lock[2]).

Position of NO_2 groups	2	3	4	2,4	2,6	2,4,6	H
Yield	63	50	74	70	100 (2 hrs.)		18

The general accelerating effect of the NO_2 group was even greater than that of the Cl group with the exception that the o-chloro- reacted faster than the o-nitrobenzaldehyde.

The trinitro derivative splits out HCOOH under the conditions of this reaction. This interesting behavior is typical of diortho-substituted benzaldehydes in the Cannizzaro reaction and will be discussed later.

Position of CH_3 group	2	3	4	2,6	2,4,6
Yield	all lower than benzaldehyde			none	7-8% under forced conditions

The exceptional behavior of the methyl derivatives has not been attributed to steric hindrance because the yield is lowered regardless of the position of the group; that is, even meta and para substitution produce a retarding influence. It is interesting to note that mesityl aldehyde gives 2,4,6-trimethylcinnamic ester by a smooth reaction in the Claisen condensation.

General conclusions: The reaction tendency of diortho-substituted benzaldehydes (except CH_3) in the Perkin reaction increases with the weight of the ortho substituents contrary to the hypothesis of steric hindrance. Evidently stereochemical influence of the substituents is masked by their exalting power on the reactivity of the CHO group.

Cannizzaro Reaction: Studies by Lock[8] on the behavior of substituted benzaldehydes in the Cannizzaro reaction have shown that the reaction may take one of two possible courses depending on the position and nature of the substituents. In general, those deriva-

[illegible]

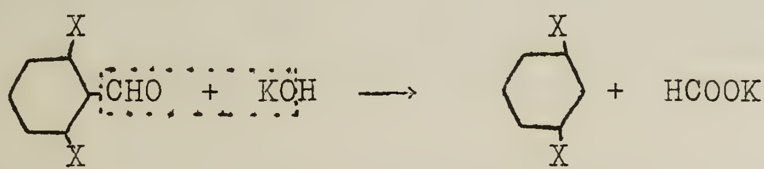
tives containing a single ortho substituent (OH is an exception) will give normal disproportionation, while diortho-substituted derivatives, under the influence of alkali, lose the CHO group as formic acid and form substituted benzene derivatives. These two types of reactions, with their exceptions, will be discussed separately.

A. Normal disproportionation: The usual Cannizzaro reaction is observed with all derivatives studied which have a free ortho position with the exception of o-hydroxy- and p-hydroxybenzaldehyde, and those derivatives containing two nitro groups (e.g. 2,4-dinitrobenzaldehyde).

o-Hydroxy- and p-hydroxybenzaldehyde are unchanged by alkali solution; with m-hydroxy derivatives normal disproportionation takes place as long as only one ortho substituent is present.

Some evidence of hindrance due to size of the group is observed by comparing bromo and chloro derivatives of the same parent compound. 3,5-Dimethoxybenzaldehyde gave complete disproportionation in one-half hour; 2-chloro-3,5-dimethoxybenzaldehyde was complete in 3 hours while 2-bromo-3,5-dimethoxybenzaldehyde required 8 hours for complete reaction.

B. Removal of CHO group: This type of reaction, which may be illustrated as follows,



is observed with all derivatives of benzaldehyde which contain two halogen atoms or one halogen atom and one nitro group or two nitro groups in the positions ortho to the aldehyde group, and aldehydes with nitro groups in the 2,4-positions. Exceptional behavior is shown by derivatives with p-hydroxy, or o-amino substituents.

This reaction in the aromatic series, which seems to depend on the position and especially on the nature of the substituents present in addition to the aldehyde group, is very similar to that observed in substituted acetaldehydes (e.g. trichloro-, tribromo-, and triphenylacetaldehyde).

$$Cl_3CCHO + KOH \longrightarrow Cl_3CH + HCOOK$$

In this reaction, the otherwise very resistant C-C bond seems to be so weakened by the presence of many negative substituents that the cleavage can take place. That weight is not the only factor is emphasized by the fact that propiolaldehyde, with very low molecular weight, gives the split with alkali to form acetylene and potassium formate.

In the aromatic series, it is obvious that, in addition to the "negative effect", the substituents in the ortho positions have some effect, especially in view of the fact that 2,4-dihalogen derivatives

give normal disproportionation even though they have two halogen atoms present.

Nearly all cases of 2,6-dihalogen substitution gave a practically quantitative yield of formic acid. The amount of formic acid produced was determined by the reduction of $HgCl_2$ to Hg_2Cl_2 (Franzen and Greve[9]).

$$HCOOH + 2\ HgCl_2 \longrightarrow CO_2 + 2\ HCl + Hg_2Cl_2$$

The effect of ortho and para hydroxyl groups is shown by the following examples. o-Hydroxy- and p-hydroxybenzaldehyde give no reaction with aqueous alkali. 2,4,6-Trihydroxybenzaldehyde, when treated with KOH, gives phloroglucinol and carbon dioxide but no formic acid. Likewise, the 2,4-dihydroxybenzaldehyde gives resorcinol (71.6%), hydrogen (74.3%), carbon dioxide, and a very small amount of formic acid (0.9%). 2,6-Dibromovanillin gave no formic acid but the 2,6-dibromo-3,4-dimethoxybenzaldehyde formed by methylation of the p-hydroxyl group induced smooth splitting to formic acid and 3,5-dibromoveratrol. From this we conclude that a free hydroxyl group in the para position not only hinders normal disproportionation to the acid and alcohol but also the elimination of the aldehyde group in 2,6-dihalogen substituted aldehydes. A hydroxyl group in the meta position hinders neither type of reaction.

A similar restraining influence is shown by 6-substituted 2-aminobenzaldehydes. 2-Amino-3,6-dichlorobenzaldehyde, when treated with KOH, gave no formic acid. However, the recovered aldehyde could be diazotized and converted to 2-iodo-3,6-dichlorobenzaldehyde which then underwent conversion to formic acid and 1-iodo-2,5-dichlorobenzene.

The effect of two nitro groups is shown in 2,4-dinitro-, 2,4-dinitro-3-methoxy-, and 2,4-dinitro-3-hydroxybenzaldehyde, all of which gave formic acid. 2,4,6-Trinitrobenzaldehyde gives formic acid and trinitrobenzene when treated with alcohol, aniline, ammonia, or dilute alkali.

The combined effects of ortho nitro groups and para hydroxyl group is shown by a comparison of the 2,6-dinitro-3-methoxybenzaldehyde with 2,6-dinitrovanillin. Under the influence of 5% NaOH the former gives 87.5% formic acid while the latter gave only 60%.

Evidence of steric hindrance due to the size of the diortho substituents is indicated by the following sequences which give the relative rates of reaction:

1. For 2,6-dihalogen substituted derivatives:

2,6-dinitro > 2,6-dichloro > 2,6-dibromo > 2,6-difluoro (gave slight disproportionation)

2. For 2,6-dihalogen-3,5-dimethoxy derivatives:

2,6-dinitro > 2-bromo-6-nitro > 2,6-dichloro > 2,6-dibromo

This order parallels the decrease in size of the groups as determined by x-ray data and also the relative interference effects of these

groups on the rates of racemization of biphenyls[10].

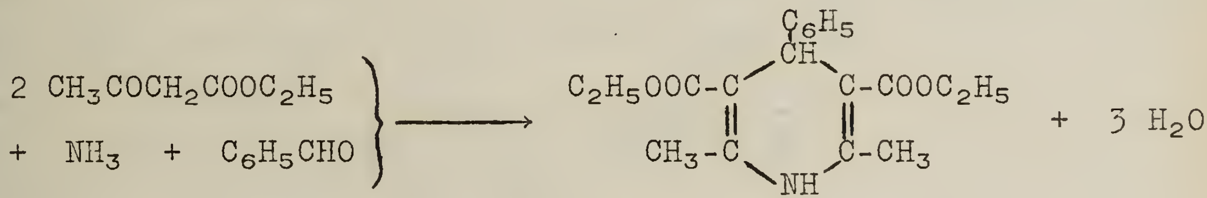
One other study on the Cannizzaro reaction deserves mention. Weissberger and Haase[11] concluded from a study of the reaction that a relationship exists between the rate of Cannizzaro reaction of aldehydes, RCHO, and the dissociation constants of the corresponding acids, RCOOH. With ortho-substituted aldehydes the reaction is slower than would be expected from dissociation constants, thus indicating the operation of another factor, presumably steric hindrance.

Addition of HCN and Stability of Resulting Cyanohydrins: Heller[12] reported that in the reaction of HCN on benzaldehyde derivatives the substituents have the power to hinder or facilitate addition. With o-nitrobenzaldehyde the addition takes place only with the aid of bisulfite in concentrated solution.

Lapworth and Manoke[13] have studied the rates of dissociation o the cyanohydrins of substituted benzaldehydes.

They report that the effect of ortho substituents examined (other than OH) is such as to depress the dissociation constants of the cyanohydrins, and that this is in direct contrast to the result to be expected from the classical "space-occupation" hypothesis used so frequently to account for the other effects associated with ortho substitution.

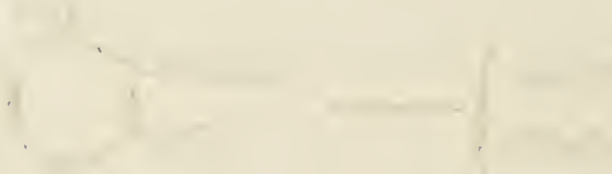
Hantzsch's Condensation: Hinkel, Ayling and Morgan[14] have studied the effects of various substituents in the Hantzsch condensation:



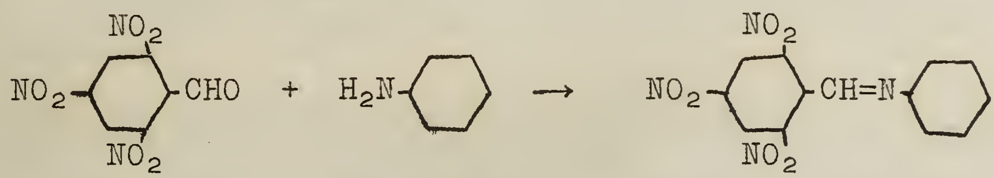
They make the following generalization: with each substituent the yield is lowest for the ortho derivative and, while the difference between the ortho and para compounds is small, there is definite evidence of a steric or ortho effect.

The greatest hindrance was observed with 2-methyl-, 2,4,6-trimethyl-, and 3,5-dinitro-2,4,6-trimethylbenzaldehyde. In the latter two cases less than 1% yields were obtained and in the 2-methylbenzaldehyde only 8.5% as contrasted with 74% for benzaldehyde. It is interesting to note that methyl groups, regardless of position, reduced the yields.

Grignard Reaction: Reich[5] reports that 2,6-dichlorobenzaldehyde gave excellent yields of the carbinol when treated with phenylmagnesium bromide. Lock[2] also reports failure to observe any hindrance when pentachlorobenzaldehyde was treated with CH_3MgI or C_6H_5MgI. Both gave the corresponding carbinol in good yields despite the great insolubility of the aldehyde in ether.



Formation of Anil: Hantzsch[15] has shown that benzaldehydes will not react with diortho-substituted aniline derivatives. Reich[5], however, has shown that diortho-substituted benzaldehydes will react smoothly with aniline.



This reaction was also successful with 2,6-dichloro- and 2,4,6-trimethylbenzaldehydes. Gattermann[16] has used this reaction to separate the mesityl aldehyde from the reaction mixture in which this aldehyde was prepared.

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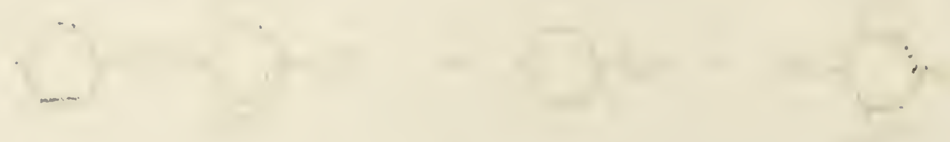
Reported by R. V. Lindsey, Jr.
April 12, 1939



RELATION OF BASICITY AND SOLUBILITY TO THE TOXICITY OF AMINES

Kindler -- Chemische Staatsinstitut der Universität Hamburg

Kindler, in considering amines as agents for the specific treatment of diseases caused by protozoa, has made a systematic survey of the toxicity of practically all available types of organic nitrogen compounds.

A method for measuring the toxicity was desired, so Kindler and his coworkers devised the following method. One cc. of a water solution of the amine (or it s hydrochloride) was mixed with an equal volume of culture solution containing paramecia. The time required for 90% or more of the organisms to be killed was then measured. The toxicity number (TN) is the reciprocal of the concentration of the original amine solution in milligrams, multiplied by the reciprocal of the time in minutes. To obtain reproducible results the strength of the solution must be adjusted so that this time lies between one and ten minutes. The culture solution was adjusted so that one cc. contained a constant number of paramecia. Since the resistance varies with different cultures, the TN of quinine was measured with each series and the TN of the other amines calculated relative to quinine = 1000 and this was called the relative toxicity number (RTN). This admits comparisons between series.

It was found in preliminary tests that the RTN with paramecia compared very nicely with the RTN for pathogenic protozoa, thus allowing the convenient substitution of paramecia for the pathogens. The RTN in this resport are the values for paramecia only.

Hydrolysis of salts is an important factor in toxicity. It is shown in Table 1 that free amines are much more active than their hydrochlorides. Table 2 shows that the weaker the amine, the more hydrolysis will occur, therefore the more toxic the salt will be.

Table 1

p-$HOC_6H_4CH_2CH_2NH_2$	60	p-$HOC_6H_4CH_2CH_2N(CH_3)_2$	400
—·HCl	1	—·HCl	1
$C_6H_5CH_2NH_2$	1000		
—·HCl	2		

Table 2

HCl salt of:	pH	RTN on dilutions of 1-100	1-500	1-2000	1-4000
p-$FC_6H_4CH_2N(C_2H_5)2$	8.72	60	50	25	—
p-$BrC_6H_4CH_2N(C_2H_5)_2$	5.11	70	200	650	1000
p-$IC_6H_4CH_2N(C_2H_5)_2$	4.99	100	400	1100	1500

The rest of this paper deals with solubility relationships. Kindler postulates that the more soluble a substance in the lipoidal material of the cell, the more toxic it will be. The following generalizations and tables are offered to support this theory.

1. In homolgous series water solubility decreases with increas-

ing chain length and the toxicity sharply increases (Table 3).

Table 3

R	R_2NH	$C_6H_5CHRNH_2$	$C_6H_5CH_2NHR$
CH_3	—	6	—
C_2H_5	—	30	—
$\underline{n}$-C_3H_7	—	130	40
$\underline{n}$-C_4H_9	25	500	75
$\underline{n}$-C_7H_{15}	13000	20000	3000
$\underline{n}$-C_9H_{19}	—	50000	19000
$\underline{n}$-$C_{11}H_{23}$	—	—	35000

2. Amines with straight chains are less soluble in water than their branched isomers (Tables 4 and 5).

Table 4

R in $C_6H_5CH_2NHR$	No. of C atoms	RTN
$CH_3(CH_2)_9$	17	30000
$(CH_3)_2CH(CH_2)_3CH(CH_3)(CH_2)_2$	17	16000
$CH_3(CH_2)_{11}$	19	40000
$CH_3(CH_2)_8CH(CH_3)CH_2$	19	10000

Table 5

	No. of C atoms	RTN
$C_6H_5NH(CH_2)_9CH_3$	17	30000
$C_6H_5N(CH_2CH_2CH_2CH_3)_2$	17	500
$C_6H_5NH(CH_2)_{11}CH_3$	19	40000
$C_6H_5(CH_2)_3N(CH_2CH_2CH_2CH_3)_2$	19	4000
$C_6H_5CH_2NH(CH_2)_7CH_3$	15	13000
$C_6H_5(CH_2)_3N(CH_2CH_2CH_3)_2$	15	300

3. Di-aryl-aliphatic amines are much less soluble in water than the primary amine and therefore are more toxic to paramecia (Table 6).

Table 6

	RTN when n =			
	1	2	3	4
$C_6H_5(CH_2)_nNH_2$	2	20	80	150
$C_6H_5(CH_2)_nN(CH_3)_2$	2	—	50	—
$(C_6H_5(CH_2)_n)_2NH$	300	600	—	—

4. Amines of the benzene series dissolve to a greater extent in water than the corresponding naphthalenes (the members of Table 7 are chosen from about 20 compounds).

Table 7

R = an alkyl group	RTN
$C_6H_5CHRCH_2NH_2$	1000 - 15000
β-$C_{10}H_7CHRCH_2NH_2$	2000 - 33000

5. The hydrochlorides of tertiary amines with two methyls on the N atom are less toxic than the corresponding primary amine salts (Table 8).

Table 8

R in $C_6H_5\overset{CH_2R}{|}CHCH_2X \cdot HCl$	RTN when X = NH_2	RTN when X = $N(CH_3)_2$
$3,4-(CH_3O)_2C_6H_3$	1000	800
p-$CH_3C_6H_4$	10000	3200
p-C_6H_5-O-C_6H_4	15000	4500

6. The toxicity of the phenyl, cyclohexyl, and n-hexyl groups give increasing toxicity to the amine in the order given (Table 9).

Table 9

R in p-R-C_6H_4-$CH(CH_3)NH_2$	RTN
C_6H_5	4000
C_6H_{11}	10000
n-C_6H_{13}	20000

7. Naturally occurring alkaloids with a few exceptions are relatively non-toxic to paramecia (Table 10).

Table 10

Alkaloid	RTN
Atropine	10
Heroin	10
Morphine	10
Apomorphine	330
Lobelin	1000
Quinine	1000

Those amines shown to be highly toxic to protoxoa by this survey are to be thoroughly tested in warm-blooded aminals for toxicity to the hosts. It is hoped some efficient synthetic therapeutics will be discovered in this manner.

Some of Kindler's preparative methods are briefly outlined below:

1. Reduction of amides catalytically or electrolytically at a lead cathode
   a. $RCONH_2 \longrightarrow RCH_2NH_2$ 65%

   b. $RCONR_2 \longrightarrow RCH_2NR_2$

2. Reduction of nitriles

   a. $ArCN \xrightarrow{H_2,\ cat.} ArCH_2NH_2$

   b. $RCHO + HCN \longrightarrow RCH(OH)CN \xrightarrow{Ac_2O} RCH(OAc)CN \xrightarrow{H_2 + cat.}$

   $$RCH_2CH_2NH_2$$

c. ArCOCl + HC $\longrightarrow$ ArCOCN $\xrightarrow{H_2,Pt}$ $ArCH(OH)CH_2NH_2$

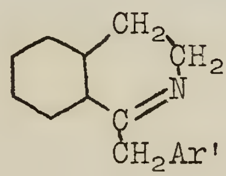
d. $ArCH_2CN$ + $(C\ H_5)_2NH$ $\xrightarrow{H_2\ +\ cat.}$ $(ArCH_2CH_2)_2NH$ in 50% yield; some $ArCH_2CH_2N(C_2H_5)_2$; remainder primary amine

e. 2 $ArCH_2CN$ $\xrightarrow[H_2SO_4\ cat.]{H_2}$ $(ArCH_2CH_2)_2NH$ 90% or above

3. Hypohalogen degradation of amides

<u>p</u>-$CH_3OC_6H_4CH_2CH_2CONH_2$ $\xrightarrow[KOH]{KOCl}$ <u>p</u>-$CH_3OC_6H_4CH_2CH_2NH_2$ 90%

4. $Ar'CH_2COOH$ + $H_2NCH_2CH_2Ar$ $\xrightarrow[tetralin]{boil}$ $Ar'CH_2CONHCH_2CH_2Ar$ $\xrightarrow[POCl_3]{benzene}$



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Reported by J. H. McCracken
April 12, 1939

THE USE OF METALLIC COMPLEXES IN THE DETERMINATION OF CONFIGURATION

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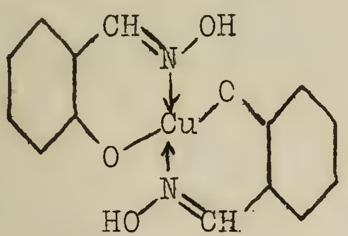
The metals of Group VIII and adjacent groups of the periodic table form complexes with certain oximes, hydrazones, and oxime-hydrazones of 1,2-diketones. Complex formation, in some cases, can be used to determine the spatial arrangement of the groups in these compounds, since only those with favorable configurations will form a complex. In view of this Hieber and Sonnekalb distinguished between the isomers of benzilphenylosazone by studying the complexes formed with stannic chloride. The methods has been extended to the other types of compounds mentioned.

<u>Oximes</u>: Salicylaldoxime forms two complexes with copper, which are shown by I and II. The product obtained depends upon experimental conditions. Hence the oxime must have the anti configuration.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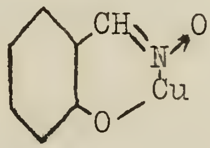
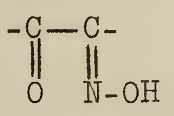
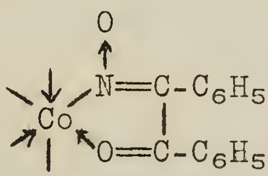
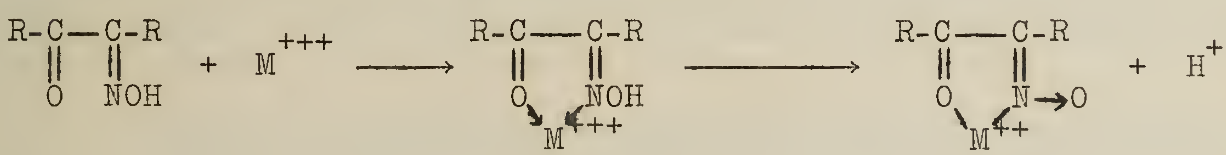

II

The monoximes of 1,2-diketones have been shown to form complexes provided their structure is given by III. An example is the complex formed by the action of three molecules of α-benzilmonoxime with cobalt, IV.

III


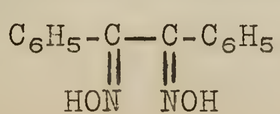

IV

The mechanism appears to be the following:



The β-oxime cannot form a complex because the position of its hydroxyl group prohibits the preliminary stage.

α-Benzildioxime, V, gives a series of complexes, VI, while the =-isomer gives none.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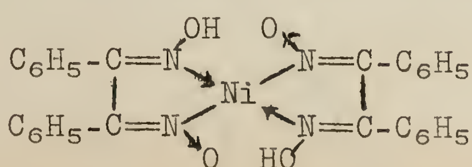
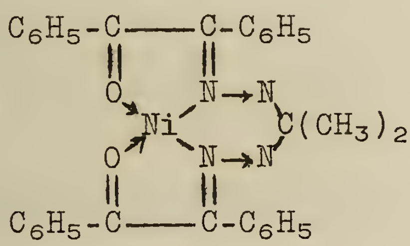
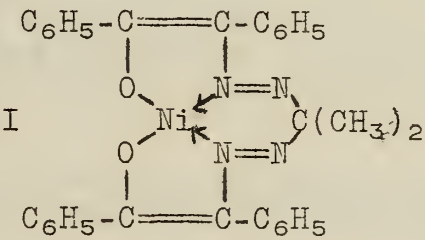
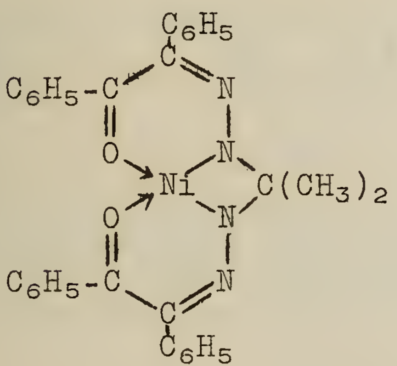

VI

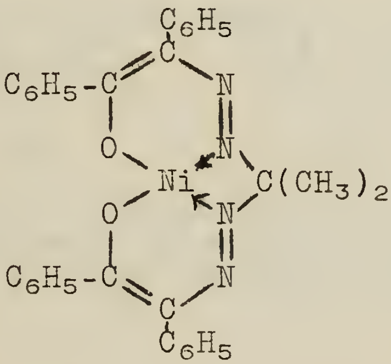
Hydrazones: The complex formed by the action of benzilmonohydrazone upon nickel acetate has the composition R_3Ni_2 where R = $C_6H_5COC(C_6H_5)=NNH-$. The complex is amorphous, slowly attacked by hydrogen sulfide, unaffected by potassium cyanide, and is decomposed by nitric acid to give benzil or benzoylketazine depending upon the conditions used. The comples presents no true analogies to those of the oximes and is much less stable than the latter.

An unusual reaction takes place when the nickel complex of benzilmonohydrazone is prepared in boiling acetone solution. A new complex is formed, called the azine complex, that contains two benzilmonohydrazone residues, one acetone residue, and a nickel atom. This is the only hydrazone complex that was obtained in crystalline form. Of the four possible structures, VII and VIII are preferable for stereochemical reasons.

VII 

VIII 

IX 

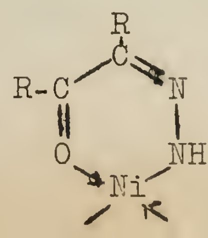
X 

Formation of the azine complex does not clear up the stereochemical problem since IX or X might be possible in view of the unusual behavior of camphorquinone monohydrazone as explained below. The reaction shows that the hydrazone complex must contain reactive imino groups. This is probably the cause of its indeterminate and unstable nature.

Tertiary-butylglyoxal monohydrazone also forms a complex with nickel acetate with the formula R_3Ni_2. It is more unstable than those just described.

The β-monohydrazone of camphorquinone gave an indication of complex formation, while the α-isomer did not. Since the configuration of the former has been shown to be XI, the complex presumably has the structure XII.

XI 

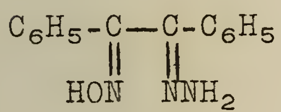
XII 

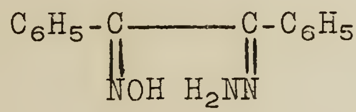
This behavior is unexpected since β-benzilmonoxime forms no complexes and is known to have a configuration corresponding to XI.

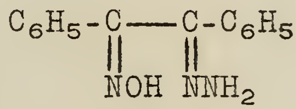
Salicylaldehydehydrazone, of which only one form is known, forms complexes with copper, nickel, cobalt, and iron. However, these complexes present no true analogy to the corresponding oxime complexes, and no deduction as to the configuration of the hydrazone can be made from their behavior. This is probably due to the presence of two nitrogen atoms in the hydrazone group, either of which may coordinate with a metal atom so that the complex formed is of the chain type.

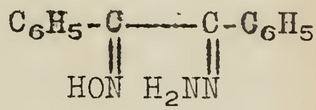
In general, the attempts to determine the stereochemical configuration of the hydrazones by means of metallic complexes were not successful because of the instability and difficulty of purification of the products. This is in contrast to the oxime complexes which have shown to be useful in this way.

<u>Oxime-hydrazones</u>: Theoretically, benzil oxime-hydrazone has four possible configurations as shown below. Only two of these are known.

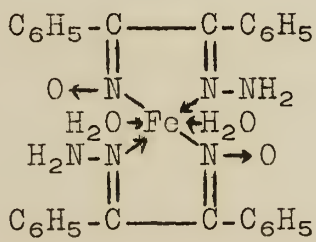

XIII


XIV


XV


XVI

α-Benzilmonoxime reacts with hydrazine to give a compound that is assigned the structure shown by XIII. This compound combines with several metals to form complexes, of which the most characteristic is the magenta ferrous compound XVII.


XVII

The oxime-hydrazone prepared from β-benzilmonoxime does not form such complexes, and is assigned configuration XIV. The configuration of the oxime group is known from earlier complex studies, and since the physical properties of the oxime-hydrazones vary in the same manner as the α- and β-dioximes the above assignment is thought to be correct. The β-dioxime forms no complexes, but the α-dioxime forms very stable complexes with nickel and palladium. This evidence does not exclude formula XV as a possibility for the β-oxime-hydrazone. The two unknown oxime-hydrazones are very probably the amphi-compounds XV and XVI.

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Reported by Wm. H. Sharkey
April 19, 1939

ORGANIC COMPOUNDS CONTAINING SELENIUM

AND TELLURIUM

Behaghel -- University of Giessen
Morgan -- University of Birmingham

Several different types of organic compounds containing Se and Te have been prepared but no very general study has been made on them. Generally the same type compounds may be made from Se and Te as can be made from O and S. However, the basicity of the compounds increases in going from O to S. The latest work has been done on the organo-selenium and tellurium halides.

The laiphatic seleno- and telluro-mercaptans are relatively unimportant and have not been studied very extensively. Shaw and Reid prepared C_2H_5SeH and tried the reactions given below, which show it to react practically the same as the -SH and -OH compounds.

$$C_2H_5Br + Na_2Se_2 \longrightarrow C_2H_5\text{-}Se\text{-}Se\text{-}C_2H_5 \xrightarrow[(O)]{(H)} C_2H_5SeH$$

$$C_2H_5SeH \xrightarrow{(CH_3)_2CO} (C_2H_5Se)_2C(CH_3)_2$$

$$C_2H_5\text{-}Se\text{-}Se\text{-}C_2H_5 \xrightarrow{Br_2} C_2H_5SeBr_3$$

$$C_2H_5SeH \xrightarrow{HBr\ -\ (O)\ -\ air} C_2H_5SeBr_3$$

$$C_2H_5MgBr \xrightarrow{Se} C_2H_5SeMgBr \xrightarrow{HBr} C_2H_5SeH$$

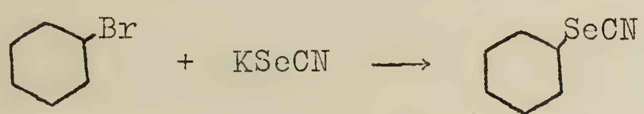
$$Na(C_2H_5)SO_4 + NaHSe \longrightarrow C_2H_5SeH \quad 40\text{-}50\%$$

These mercaptans show an increase in b.p. in going from S to Te, as well as bad odors, all sol. in organic solvents.

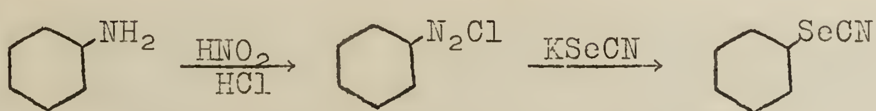
Other aliphatic compounds are the seleno- and telluro-ketones, which are made as below. They do not have the disagreeable odors of the compounds above, but are not as stable as the oxygen and sulfur derivatives.

$$(CH_3)_2C{=}O + H_2Te \xrightarrow[\text{reflux}]{HCl} (CH_3)_2C{=}Te$$

The aromatic compounds to be discussed are mainly the Aryl-SeH type and their derivatives and homologues. The best methods for preparation are given in equations A and B, the latter by the better.

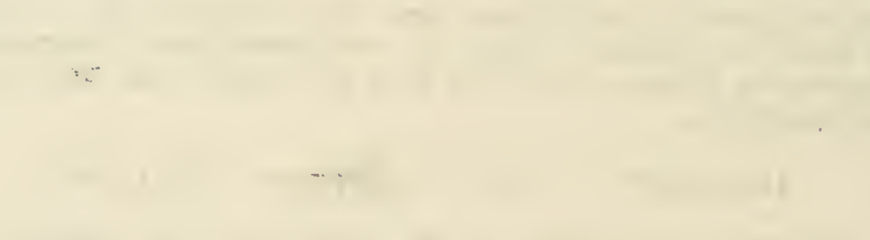


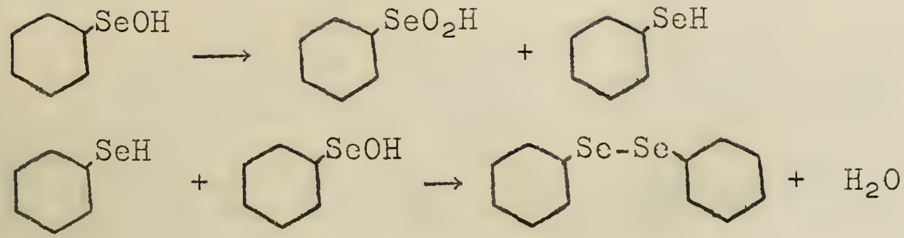
(A)



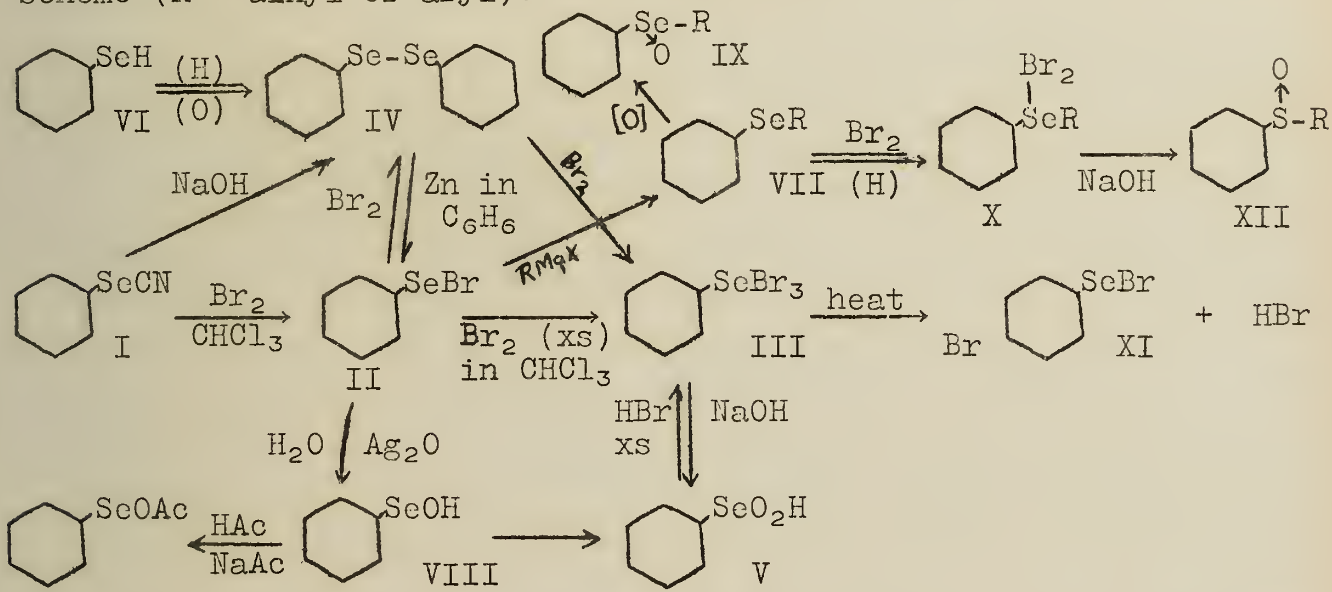
(B)

These selenocyanates cannot be directly converted to the selenophenol due to the ease of oxidation of the selenophenol.





However, indirectly one can proceed to the selenomercaptans and obtain a very good yield. The reactions are shown in the following scheme (R = alkyl or aryl):

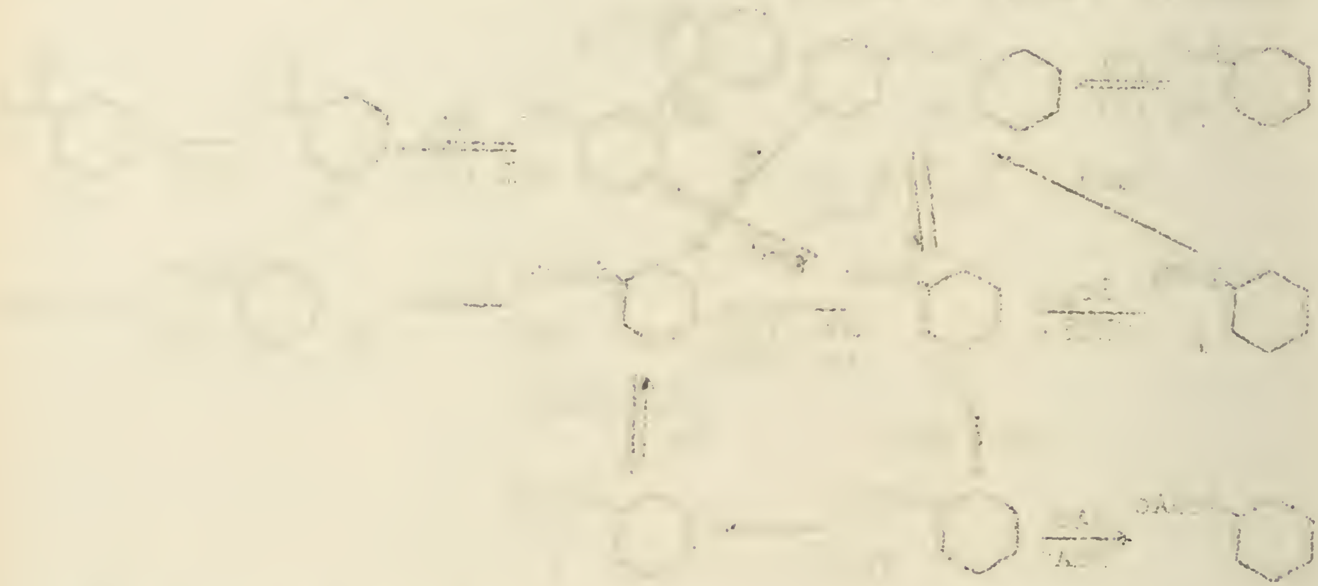


Bromine is used only as an example here and chlorine gives the same reactions, its compounds being more stable than the bromine derivatives. The iodine derivatives are all quite unstable. The dinitro and trinitro derivatives become sp electronegative that only the monohalide can be prepared, and the trihalide decomposes very rapidly.

The acids are not as important in the Se and Te series as in the S series. The selenonic $RSeO_3H$ can best be made by heating C_6H_6 with H_2SeO_4. However, it is unstable.

The tellurium compounds behave in the same manner as the Se so no chart will be included.

These reactions show that the basicity increases from O to S as evidenced by the formation of chlorides. Also the $C_6H_5S2O_3H$ will give a salt with nitric acid having the formula $C_6H_5Se(O_2)ONO_2$. These compounds have not been studied as much as S derivatives due to their odors and also because they are very poisonous.



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Reported by D. E. Burney
April 19, 1939

THE CHEMISTRY AND STRUCTURE OF LIGNIN

Hibbert -- McGill University, Montreal
Freudenberg -- Chem. Institut d. Universität, Heidelberg

I. Isolation of Lignin: Lignin has not been isolated unchanged. Whatever method is employed, a lignin preparation is obtained which is no longer identical with the natural lignin. The various methods for the isolation of lignin may be conveniently divided into two classes: 1) those that depend on the removal by hydrolysis of the cellulose and other components, leaving the lignin as an insoluble residue, and 2) those that depend on the removal of lignin from the substances with which it is associated.

Methods of Class 1:

1. Klason Sulfuric Acid Method. Ground wood is gelatinized with 66% sulfuric acid. Product is diluted with water, filtered, and washed; it is then heated on the steam bath with 0.5% HCl for 12 hrs., and finally washed and dried.

2. Willstätter Fuming HCl method: Wood is hydrolyzed with HCl producing a product called "Willstätter lignin".

3. Freudenberg's "Cuproxam" Lignin. Wood is treated with Schweitzer's reagent followed by treatment with dilute acids until residue has the same methoxyl content as "Willstätter lignin".

Methods of Class 2:

1. Sulfite Method. The delignification is brought about by heating wood with acid sulfites under pressure. Lignin is obtained as water soluble sulfonic acids.

2. Separation by Alcoholysis. Lignin is heated with various hydrolytic compounds, e.g., ethanol, butanol, ethylene glycol, phenol, etc., to form a product containing the alkyl or aryl group in combination with the lignin.

II. Constituent Groups in Lignin: The presence of methoxyl and hydroxyl groups has been definitely established in lignin. Alcoholic as well as phenolic hydroxyl groups seem to be present.

Freudenberg obtained formaldehyde upon distilling Urban's lignin with 12% HCl and accordingly advanced the hypothesis that the formaldehyde arises from a methylene dioxide grouping ($-OCH_2O-$) in the lignin. Hibbert disagrees with this hypothesis.

Klason has postulated the presence of the ethylenic bond to account for the formation of rather stable lignin sulfonic acids. Hibbert disproved this by obtaining negative results when fully methylated spruce lignin was subjected to the action of hydrogen in presence of catalysts under conditions in which reduction of open chain ethylenic linkages readily occurs.

The evidence as to presence of carbonyl is not conclusive.

III. Reactions of Lignin: 1. Acylation. Acetyl content of acetylated lignin varies considerably with the source of lignin.

2. Alkylation. Alkylation readily occurs with usual agents.

3. Halogenation. Substitution but not addition of halogens occurs. Little is known about the character of the products.

4. Nitration. Lignin is nitrated very readily leading to the conclusion that lignin is of phenolic constitution.

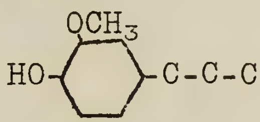
5. Sulfonation. Lignin dissolves in sulfurous acid and acid sulfites to form lignin sulfonic acids. Melander found two fractions of lignin sulfonic acids in sulfite liquor. One could be precipitated

with NaCl, called α-lignin-S-acid; the other was not precipitated with NaCl and called β-lignin-S-acid. Sulfonation proceeds in two stages. In the first stage an insoluble lignin sulfonic acid is formed, which in the presence of the cooking liquor is converted into soluble lignin sulfonic acids. Frieser showed that lignin already completely freed from polysaccharides by treatment with mineral acids undergoes autocondensation under the influence of the acid and can no longer be dissolved by sulfonation.

6. Oxidation. When lignin is subjected to oxidation even under mild conditions, complete disruption of the molecule occurs giving simple degradation products. Permanganate oxidation yields simple organic acids, as formic, acetic, oxalic, etc. Oxidation of methylated lignin yielded anisic acid and of ethylated lignin yielded p-ethoxybenzoic acid. These results indicate the presence of the following group in the molecule of lignin: p-HOC_6H_4-C-.

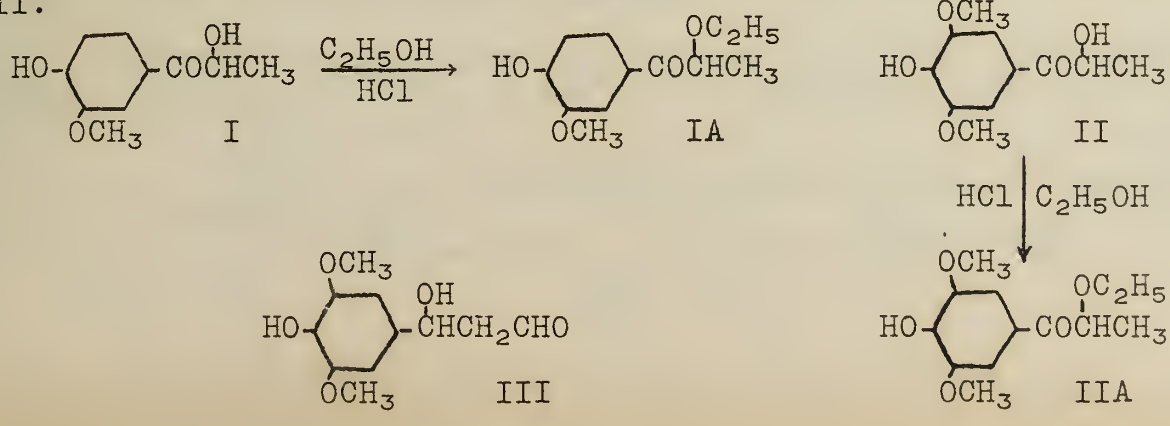
7. Zinc Dust Distillation. Philips distilled alkali lignin from corn cobs with Zn dust in an atmosphere of H_2 at less than 400°C. The following products were obtained: catechol, guaiacol, 1-n-propyl-3-methoxy-4-hydroxybenzene, and anisic acid upon permanganate oxid.

8. Dry Distillation. Dry-distilled alkali lignin from corn cobs at 25 mm. in presence of CO_2 yielded same products as in 7 and in addition, phenol, o-cresol, and 1-vinyl-3-methoxy-4-hydroxybenzene. Results of reactions 7 and 8 indicate the following two nuclei in the structure of lignin:



IV. Possible Structures of Lignin: The literature concerning the structure of lignin is now extensive and a large number of constitutional formulas have been proposed. All these formulas are more or less speculative in character, although evidence of a fragmentary character can be mustered for their support.

A. Hibbert's Structure: Hibbert subjected spruce wood meal and maple wood meal to the action of HCl and ethanol to obtain an ethanol lignin. By precipitating the ethanolysis mixture with H_2O he obtained three fractions: (1) crude water soluble oils; (2) water insoluble ethanol lignin; and (3) ethoxylated lignin left in wood residue. Fraction 1 was investigated chiefly and found to contain some readily distillable phenols and aldehydes; in addition it contained some non-distillable products which could be converted to distillable products by pressure hydrogenation. From fraction 1 of spruce wood α-ethoxypropiovanillone (IA) was obtained. From maple wood α-ethoxypropiosyringone (IIA) was also obtained, with aldehyde III.



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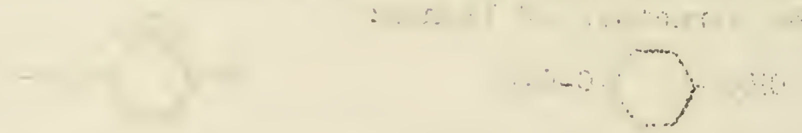

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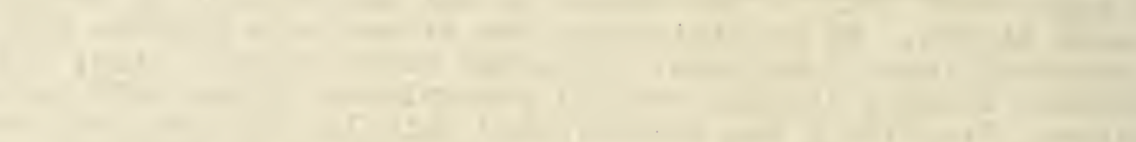
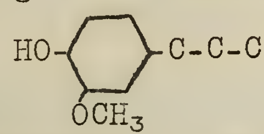
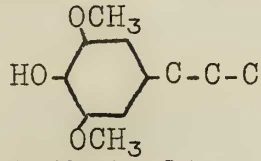
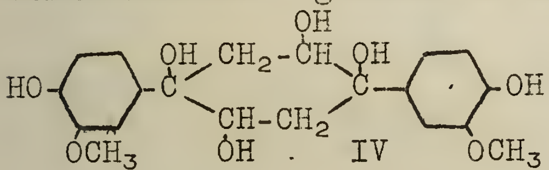


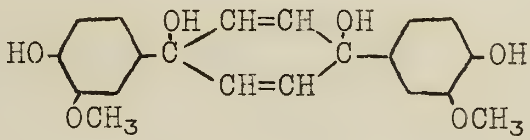
The following aromatic fission products were obtained from spruce and maple lignin sulfonic acids: vanillin, acetovanillone, guaiacol, syringic aldehyde, acetosyringone, pyrogallol 1,3-dimethyl ether. It appears that lignin is a simple condensation polymer of the following two structural units:





In this connection it can be pointed out that ultra-violet spectra of lignin and lignin derivatives indicated a benzenoid structure for lignin resembling the spectra of coniferyl alcohol and related compounds. Hibbert postulates the existence of the following types of structures in lignin in addition to the types I, II, and III:


IV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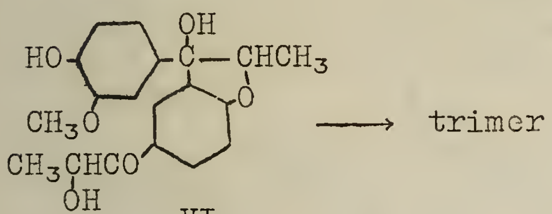
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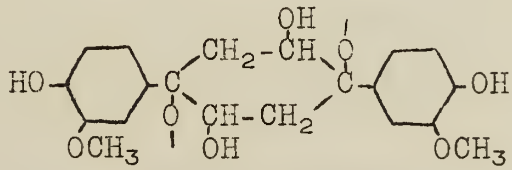
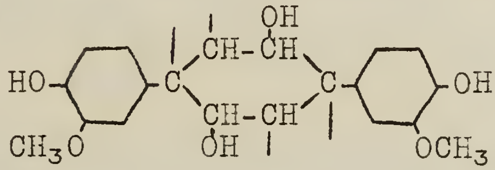
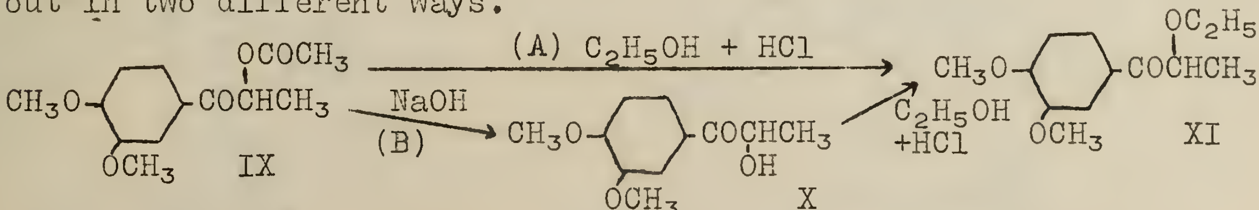

VII

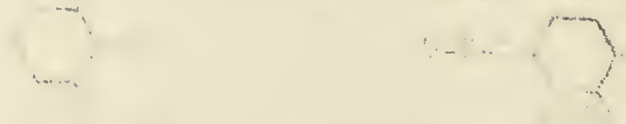

VIII

Until quite recently there has been a general tendency to ascribe a highly complex structure to lignin, but the opinion is growing that in the wood it is a simple substance of low molecular weight and which, due to its unstable character, very readily undergoes condensation-polymerization reactions yielding the more complex materials isolated in the form of "extracted" lignins. Hibbert suggests that structural typesI, II, III, IV, V, and VI probably exist in natural lignins, while in extracted lignin, types VII and VIII exist as reversible and irreversible polymers. Staudinger's molecula: weight determinations on solid lignins show that they have relatively low molecular weights and their whole behavior indicates that they are built up on a different principle than cellulose and other similar high molecular weight polymers.

Hibbert obtained α-ethoxypropioveratrone (XI) from methylated ethanol lignin. The final steps of the synthesis of XI were carried out in two different ways.

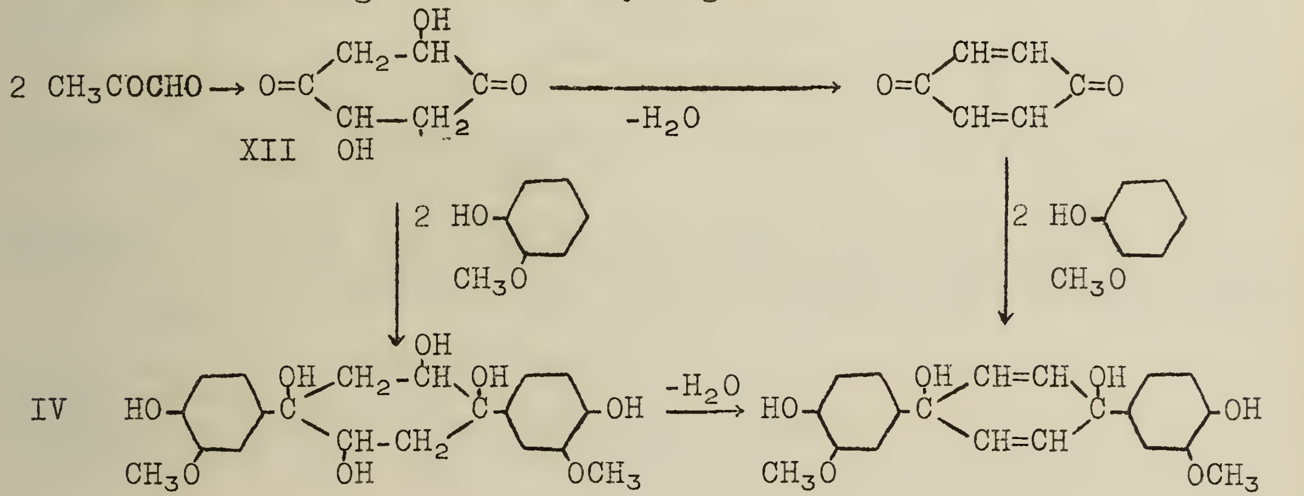


Step A gives a yield of 80% while step B gives 12%, a large amount of a polymer being formed. It is highly improbable that the α-hydroxyl

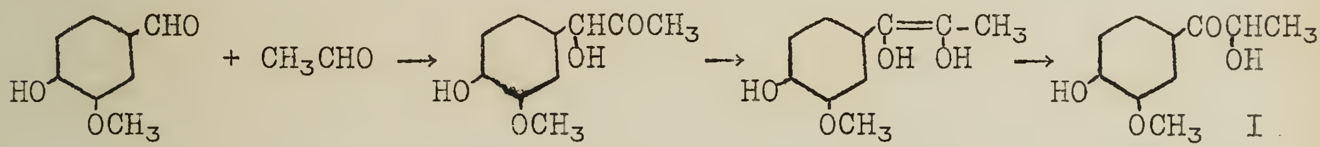


group in a building unit such as X exists free in the wood but is bound up, possibly as a glucoside. In the extraction process with HCl and ethanol an ether interchange probably occurs giving the ethoxy derivative. Hibbert showed that on warming I (related to X) with dilute H_2SO_4 it was converted into a light brown condensation product nearly identical with Freudenberg's "cuproxam" lignin.

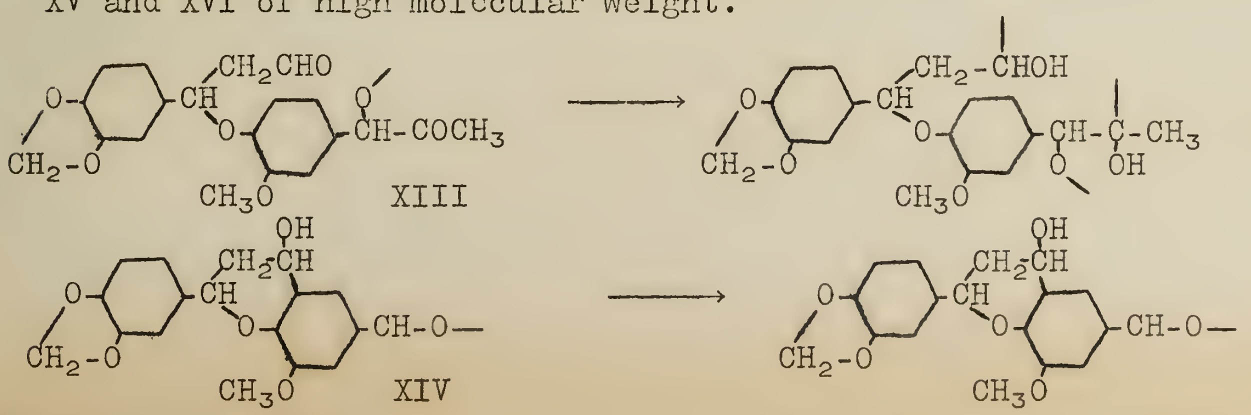
Possible Synthesis of Lignin Buidling Units in Nature: Methyl glyoxal formed during plant metabolism is postulated by Hibbert as the key substance in the formation of lignin. It is known to form a dimer of unknown structure. Possibly it is the cyclic diketone XII formed by an intermolecular aldol condensation of two moles of the methyl glyoxal. Lignin building units IV and V are then formed by condensation with guaiacol and syringone.

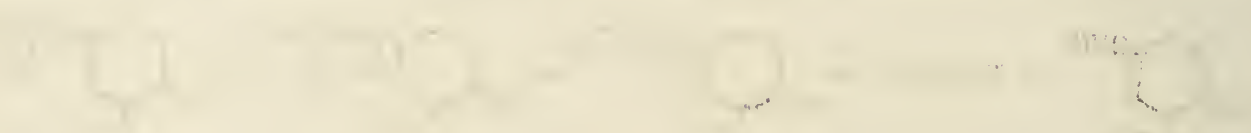

XII IV V

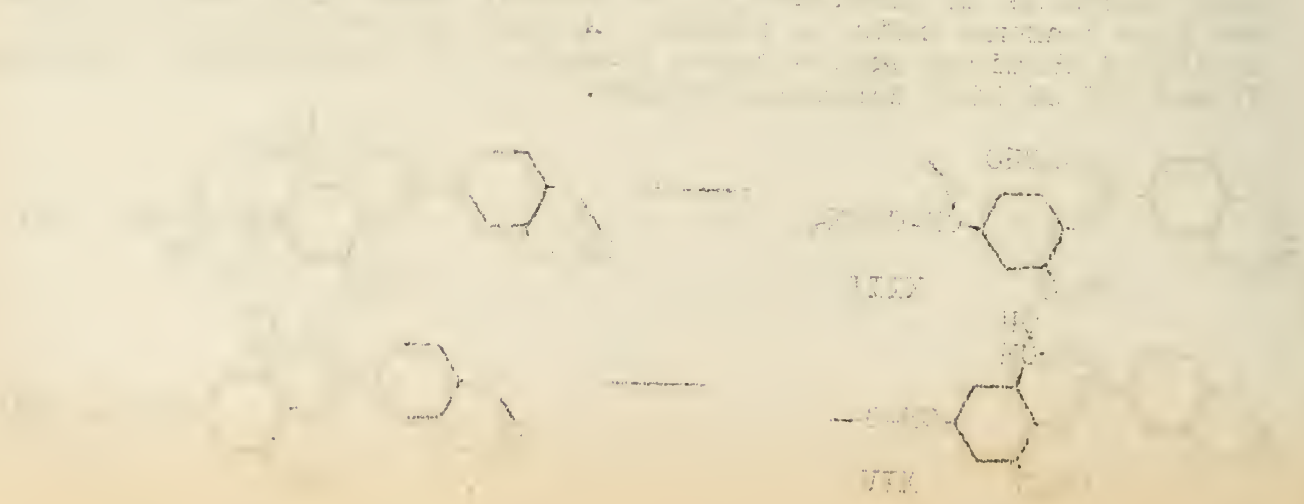
Building units I and II could be formed from vanillin and CH_3CHO through a "carboxylase" enzyme synthesis similar to Neuberg's synthesis of α-hydroxypropiophenone by the addition of benzaldehyde to a solution of glucose under vigorous yeast fermentation.


I

B. Freudenberg's Structure of Lignin: Freudenberg regards lignin as being made up of low molecular weight units which are derivatives of 3,4-$(OH)_2C_6H_3$-Pr. Primary lignin in young wood probably exists as an admixture of structural units XIII and XIV which are five benzene units in length. A post mortem condition or the action of chemical agents cause formation of 3-dimensional structures XV and XVI of high molecular weight.


XIII XV XIV XVI





C. Hilpert's Views on Lignin: Hilpert's views are drastically opposed to those of Hibbert's and Freudenberg's. He claims that "native" lignin actually does not exist in the wood but is formed as a product of the resinification of especially sensitive methylated carbohydrates when they are subjected to extraction methods. Most of the experimental evidence seems to disprove this viewpoint.

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Reported by L. A. Patterson
April 26, 1939

ALIPHATIC DIAZO COMPOUNDS AND THEIR REACTIONS WITH CARBONYL DERIVATIVES

The first aliphatic diazo compound was prepared in 1883 by Curtius who obtained ethyl diazoacetate, $CH_2N_2COOC_2H_5$, by the action of nitrous acid on the ester of glycine hydrochloride. Diazomethane was prepared by von Pechmann in 1894 by treating N-methyl-N-nitrosobenzamide, $C_6H_5CON(NO)CH_3$ or methylnitrosourethane, $CH_3N(NO)COOC_2H_5$, with alkali.

I. <u>Preparation of Diazo Hydrocarbons</u>: The diazo hydrocarbons are prepared today by several methods:

(a) From nitrosourethanes:

$$CH_3-\underset{NO}{\underset{|}{N}}-COOC_2H_5 + \text{alkali} \longrightarrow CH_2N_2$$

(b) From the amine salt:

$$CH_3NH_2\cdot HCl \xrightarrow{KOCN} CH_3NHCONH_2 + KCl$$

$$CH_3NHCONH_2 \xrightarrow{HNO_2} CH_3N(NO)CONH_2 + H_2O$$

$$CH_3N(NO)CONH_2 \xrightarrow{NaOH} CH_2N_2 + CO_2 + NH_3$$

(c) From mesityl oxide:

$$(CH_3)_2C{=}CHCOCH_3 + CH_3NH_2 \longrightarrow (CH_3)_2\overset{NHCH_3}{\overset{|}{C}}-CH_2COCH_3 \xrightarrow{HNO_2}$$

$$(CH_3)_2\underset{CH_3-N-NO}{\underset{|}{C}}-CH_2COCH_3 \xrightarrow{NaOC_3H_7} \underset{80\%}{CH_2N_2} + (CH_3)_2C{=}CHCOCH_3 + H_2O$$

(d) From hydrazine:

$$H_2NNH_2 + CHCl_3 + 3\ KOH \longrightarrow CH_2N_2 + 3\ KCl + 3\ H_2$$

Substituted diazomethanes may be prepared according to the method of Staudinger by oxidation of the hydrazones of ketones:

$$(C_6H_5)_2C{=}NNH_2 \xrightarrow{HgO} (C_6H_5)_2C{=}N{=}N \qquad 85\text{-}98\%$$

II. <u>Reactions with Carbonyl Compounds</u>:

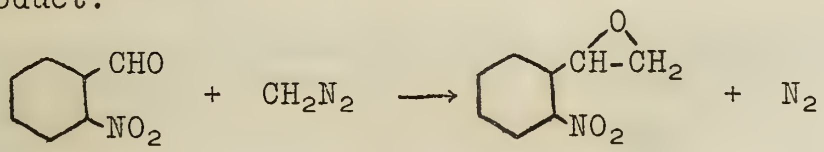
(a) <u>Aldehydes</u>: Aldehydes, both aliphatic and aromatic, behave toward diazomethane as though theu contained an active hydrogen atom and give methyl ketones:

$$\underline{n}\text{-}C_6H_{13}CHO \xrightarrow{CH_2N_2} \underline{n}\text{-}C_6H_{13}COCH_3 + N_2$$

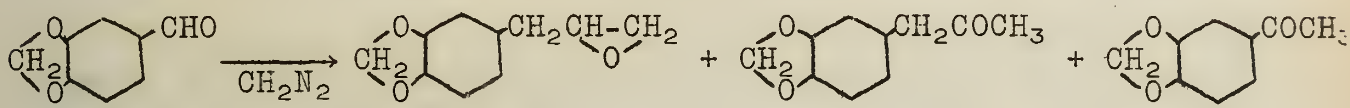
$$C_6H_5CHO \xrightarrow{CH_2N_2} C_6H_5COCH_3 + N_2$$

The homologs of diazomethane are even more reactive and accordingly almost quantitative yields of propio-, butyro-, and valerophenones have been obtained from benzaldehyde and the appropriate diazo compound.

Arndt has shown that the reaction with aldehydes is not always clean-cut, for in some cases the ketone is formed only as a by-product, the principal product being the ethylenic oxides. For example m- and p-nitrobenzaldehydes give the corresponding acetophenones but the o-isomer gives o-nitrophenylethylene oxide as the main product:



Piperonal reacts with diazomethane to give safrole oxide along with piperonyl acetone and acetopiperone:



In general it can be stated that aldehydes and diazomethane yield a mixture of methyl ketone and ethylenic oxide, the relative amounts of each depending upon the particular aldehyde involved.

(b) Ketones: Ketones are much less reactive toward diazomethane than are aldehydes. Under the proper conditions, however, they will react to give a mixture of a higher ketone and an ethylenic oxide.

$$CH_3COCH_3 + CH_2N_2 \longrightarrow CH_3COCH_2CH_3 + (CH_3)_2\underset{O}{C-CH_2}$$

$$C_6H_5COCH_3 + CH_2N_2 \longrightarrow C_6H_5CH_2COCH_3 + C_6H_5-\underset{CH_3}{C}\underset{O}{-}CH_2$$

It has been shown that alcohol or water accentuates the dipolar condition of the carbonyl group and so aids the reaction. One or the other is usually added to the reaction mixture for this purpose.

Groups which activate the carbonyl favor the formation of the ethylenic oxide. Thus Adamson and Kenner obtained an 86% yield of α-phenyl-α-chloromethylethylene oxide from ω-chloroacetophenone and diazomethane in ether and methyl alcohol:

$$C_6H_5COCH_2Cl + CH_2N_2 \longrightarrow C_6H_5-\overset{CH_2Cl}{\underset{O}{C-CH_2}}$$

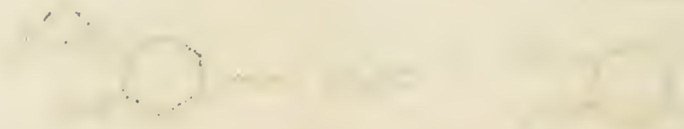
(c) Cyclic Ketones: Cyclic ketones undergo similar reactions but in this case ring enlargement takes place. For example, free diazomethane reacts with cyclohexanone with the formation of cycloheptanone and pentamethylene-ethylene oxide along with a trace of cyclooctanone:

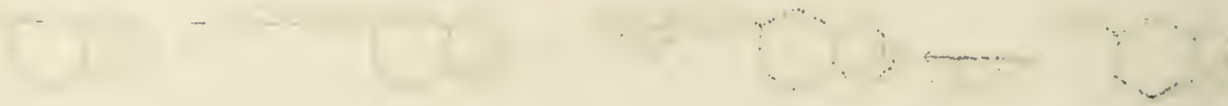
$$(CH_2)_5CO + CH_2N_2 \longrightarrow (CH_2)_2CO + (CH_2)_5{=}\overset{O}{C-CH_2} + (CH_2)_7CO$$

Cyclopentanone yields the same products as cyclohexanone. Presumably cyclohexanone is first formed and reacts further with the diazomethane

$$(CH_2)_4CO \xrightarrow{CH_2N_2} (CH_2)_5CO \xrightarrow{CH_2N_2} (CH_2)_6CO$$

Cycloheptanone gives a fair yield of cyclooctanone and some hexamethylene-ethylene oxide. Cyclooctanone is unaffected either by diazo-

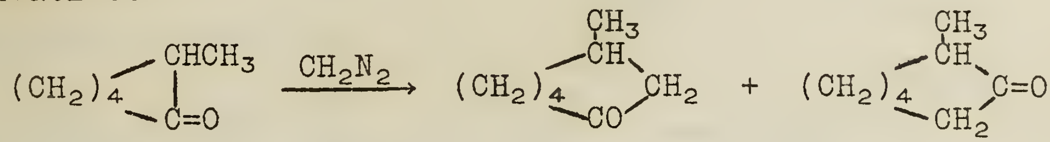




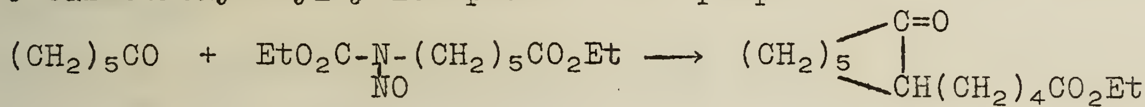
methane or by its more active homologs such as diazoethane.

However, with the other cyclic ketones mentioned the homologs of diazomethane yield substituted cyclic ketones. Thus, cyclohexanone when treated with diazoethane and diazo-n-octane yields 2-methyl- and 2-heptylcycloheptanone respectively.

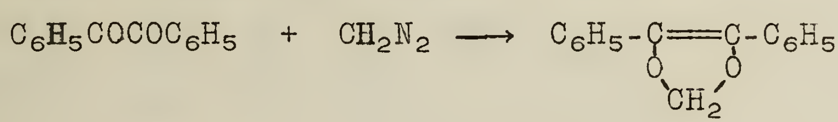
2-Methylcyclohexanone yields with diazomethane a mixture of 2- and 3-methylcycloheptanones and an equal quantity of ethylene oxide derivatives:



A further extension of this ring enlargement process made by Adamson and Kenner involves the substitution of a diazo compound having a functional group for the diazohydrocarbon. In this way 2-δ-carbethoxybutylcycloheptanone was prepared:



(d) Diketones: Aliphatic diketones such as diacetyl and acetonylacetone are not affected by diazomethane but benzil reacts to give α,β-dihydroxystilbene methylene ether:



III. Mechanism: The mechanism of the reactions of the aliphatic diazo compounds naturally entails a consideration of their structure. Curtius originally used the cyclic structure which was accepte for many years until Angeli suggested the linear formula $R_2C=N\equiv N$. Opinion was divided on the subject since work of either a physical or chemical nature led to ambiguous results.

It became obvious that the Angeli formula containing the pentacovalent nitrogen atom could not be correct and Langmuir proposed the structure $R_2C=N\overset{\rightarrow}{=}N$. Another modification of Angeli's formula, in which the middle nitrogen atom donates two electrons to the carbon atom, has been considered: $R_2C\leftarrow N\equiv N$.

Electron diffraction studies by Boersch have shown conclusively that the chain formula is the correct one, but the low dipole moment of the diazo group excludes either of the two chain formulas alone. The only difference between the two lies in the distribution of electrons and so the tendency today is to consider diazo compounds as a resonance mixture of the two electronic structures:

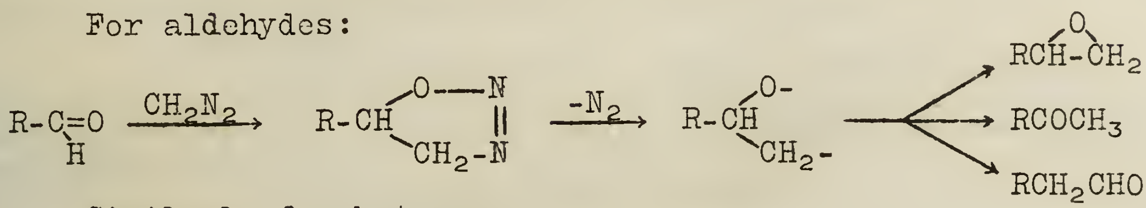
$$R_2C=N\overset{\rightarrow}{=}N \quad \Longleftrightarrow \quad R_2C\leftarrow N\equiv N$$

Either of these two structures might be expected to undergo 1,3-addition in the following manner:

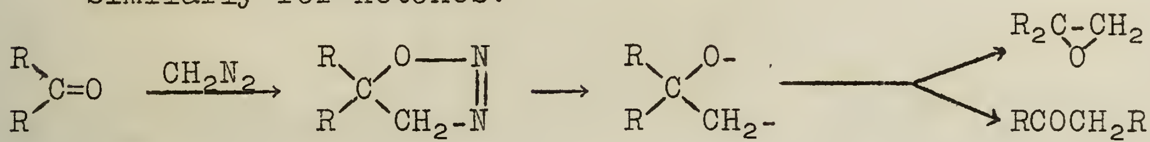
$$R_2C=N\overset{\rightarrow}{=}N \quad + \quad XY \quad \longrightarrow \quad R_2\underset{X}{C}-N=N-Y$$

Applying this to the reaction with carbonyls, the mechanism may be considered as taking place in the following manner:

For aldehydes:



Similarly for ketones:



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Reported by W. H. Rieger
April 26, 1939

SOME RECENT ADVANCES IN CHEMILUMINESCENCE

I. Introduction: Chemiluminescence may be defined as the light given off as a direct result of a chemical reaction. This discussion will be limited to those types of chemiluminescence which are produced by oxidation reactions in solution.

A. Early Work:

1. Bioluminescence: Marine animals, fireflies, etc., have all been shown to produce chemilumiscence by the action of atmospheric O_2 on a substance called "luciferin" in the presence of an enzyme luciferase.

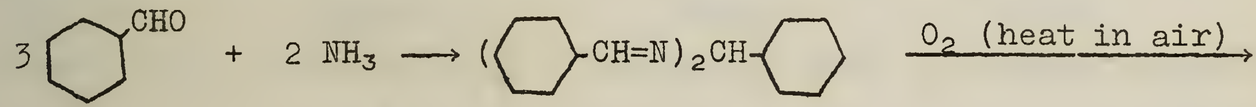
2. Yellow phosphorus in air.

3. Pyrogallol

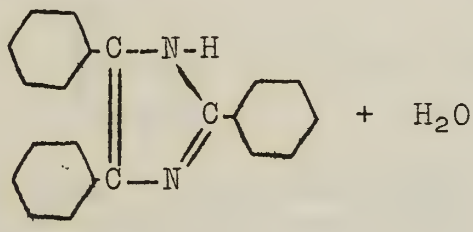
a. Enzymatic (potato juice + air)

b. $HCOH + KOH + H_2O_2$[1].

B. Lophine (triphenylglyoxaline, I): Lophine produces a good light when oxidized either by $H_2O_2 + NaClO + NaOH$[2] or by $H_2O_2 + K_3Fe(CN)_6 + NaOH$. Radziszewki[3], who discovered the luminescent properties of lophine prepared it in the following two ways:

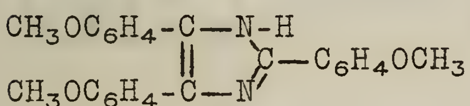


lophine (I)



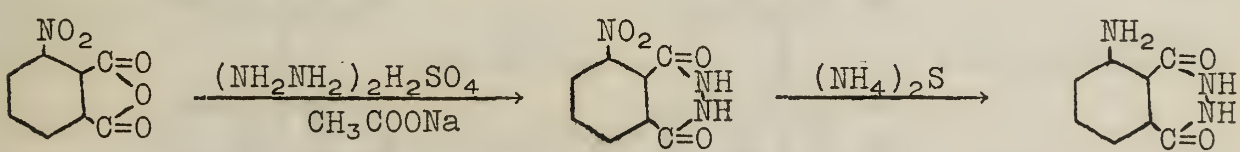
$$\begin{matrix} C_6H_5\text{-}C{=}O \\ | \\ C_6H_5\text{-}C{=}O \end{matrix} + C_6H_5CHO + 2\ NH_3 \longrightarrow I + 3\ H_2O$$

Using these two methods many derivatives gave been prepared[2]. The one that gave the best chemiluminescence was the tri-p-methoxy derivative II. Lophine, being easily prepared, is often satisfactory for demonstrations[4], although luminol is still unequaled for this purpose.



II

C. Luminol (3-aminophthalhydrazide, III): Luminol, discovered by Albrecht,[5] can be prepared as follows:[6]



III

In recent years many similar compounds have been prepared and studied. Wegler[7] reports that the alkaline diazo solution of luminol gives brighter luminescence than luminol itself.

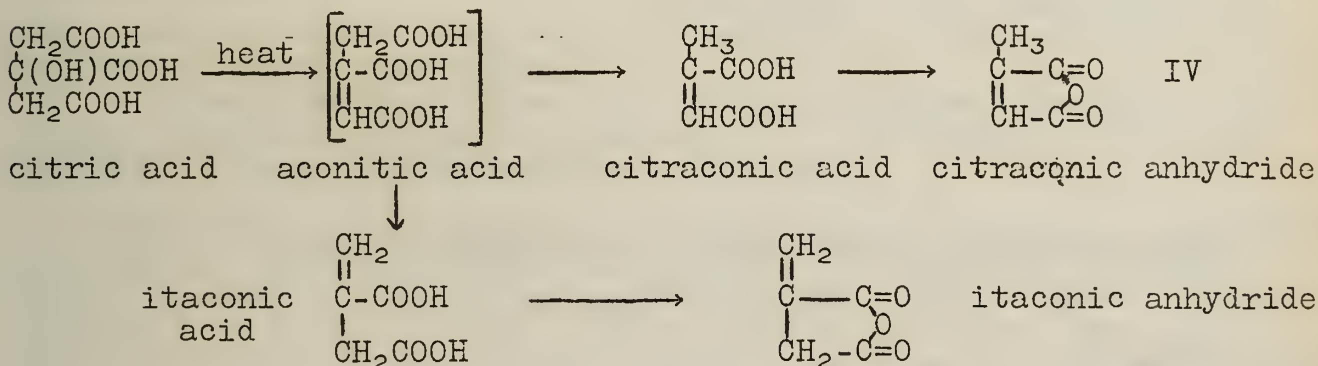
Drew and Pearman[8] after preparing and studying many derivative of phthalaz-1,4-dione conclude "that substitution of immobile groups for two of the enolizable H atoms removes the luminescence and that

the substitution even for one of them greatly diminishes, if it does not entirely remove that property".

Drew and Garwood[9] were able to isolate a peroxide ($C_8H_8O_4N_3Na$, the Na salt of 5-amino-1,4-dihydroxy-2,3-dihydrophthalazine peroxide) by the action of H_2O_2 on a basic solution of 5-aminophthalaz-1,4-dione. This peroxide gave chemiluminescence in a water solution in the presence of hemoglobin or copper salts.

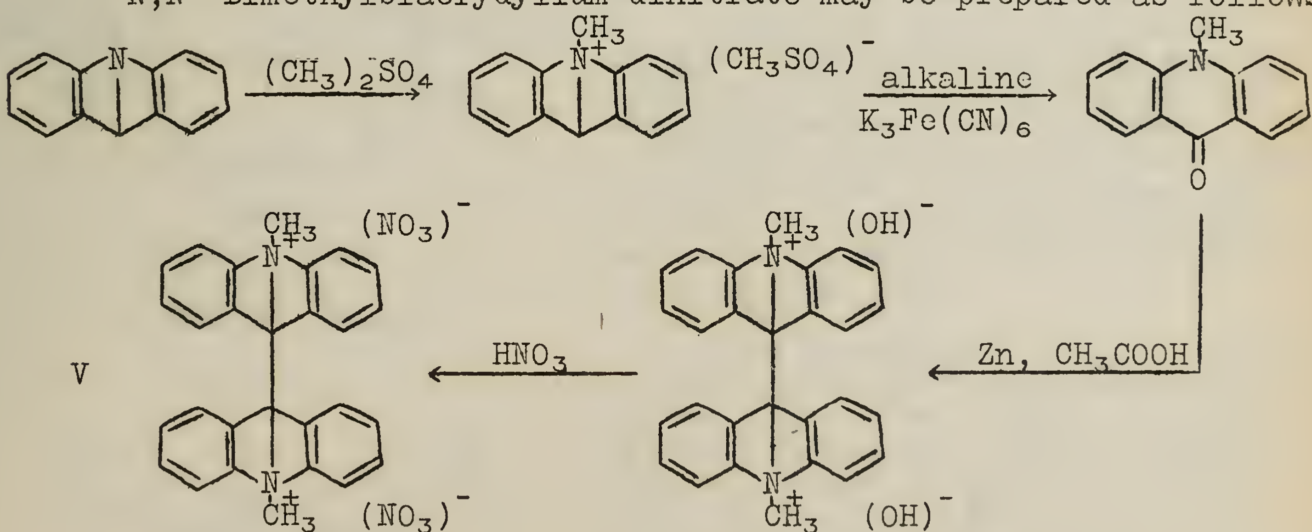
II. Some Recently Discovered Chemiluminescent Reactions:

A. Citraconic anhydride: It has been observed that the decomposition products of a large number of organic substances are chemiluminescent when oxidized. Of the many examples observed only in the case of citric acid have pure substances been isolated from the decomposition products and tested for chemiluminescence. Of the substances isolated only citraconic anhydride (IV) gave chemiluminescence.

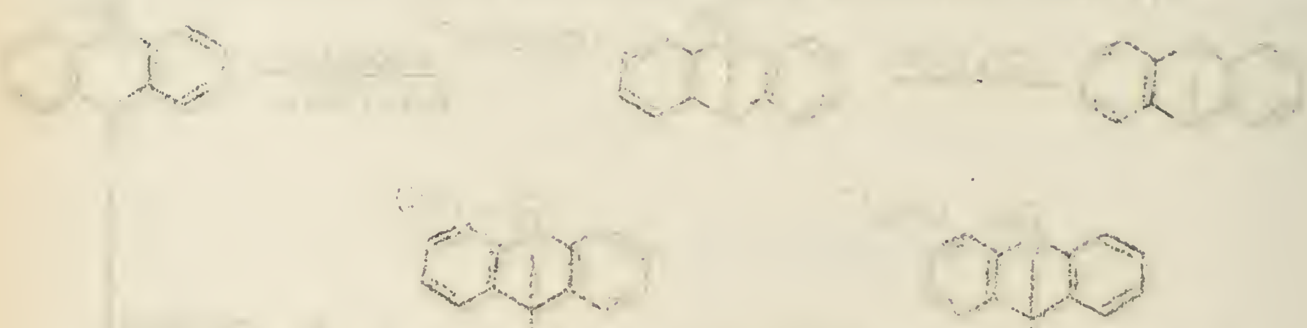


B. Biacridylium salts: Glen,[10] Glen and Petsch,[11] and Decker and Petsch[12] have shown that N,N'-dimethylbiacrydylium dinitrate (V) will give a very bright chemiluminescence when allowed to react with H_2O_2 in an alkaline solution. A few drops of OsO_4 solution is reported to increase greatly the brightness of the light at the expense of its duration. These workers report that this is the brightest case of chemiluminescence known, even brighter than luminol

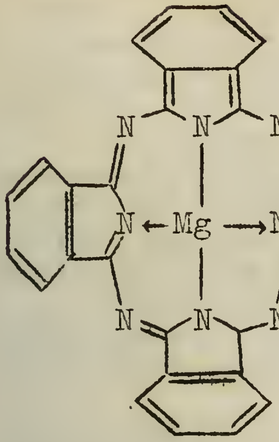
N,N'-Dimethylbiacrydylium dinitrate may be prepared as follows



C. Complex magnesium compounds: Helberger,[13] and Helberger and Hever[14] have recently reported that magnesium phthalocyanine VI and many magnesium complexes of the porphyrins VII were chemiluminescent when added to boiling tetralin. They showed that

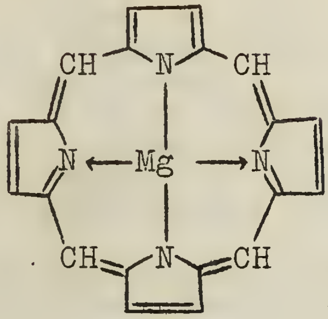


this was due to the presence of tetralin peroxide in commercial tetralin.



VI

Magnesium phthalocyanine[15]



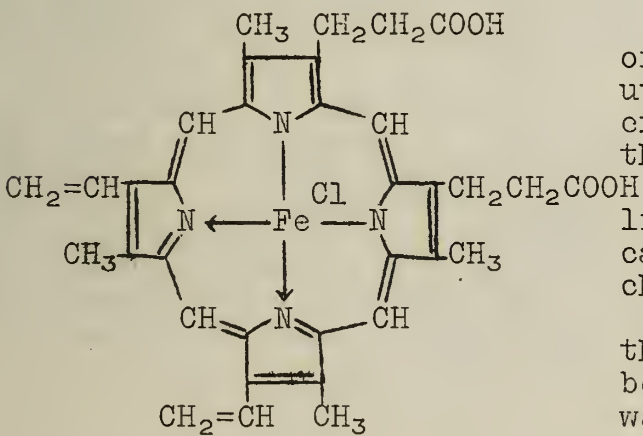
VII

Mg complex of porphyrin nucleus[15]

Rothemund[16] has shown that both chlorophyll a and chlorophyll b are chemiluminescent under similar conditions. He also worked with derivatives of the porphyrins.

It has long been known that aromatic Grignard reagents will produce chemiluminescence on oxidation.[17] The brightest one to be reported is p-chlorophenylmagnesium bromide.

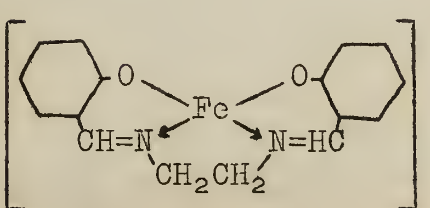
III. <u>The Use of Hemoglobin or Hemin as an Oxidizing Agent</u>: For most organic chemiluminescent reactions it is necessary for best results to have two oxidizing agents present. One of these is a peroxide such as H_2O_2, Na_2O_2, $NaBO_3$, benzoyl peroxide, etc. The other may be any one of a large number of substances such as $K_3Fe(CN)_6$ NaClO, etc., which will be reduced by H_2O_2 in basic solution to liberate oxygen.[21] One of the most interesting substances that has been used as an oxidizing agent is hemoglobin or hemin (VIII).



Hemin[18] (VIII)

Many workers have reported the use of this substance. Some have attributed its influence to a catalytic effect[19,20] but it has been found [21] that substances such as iron, iron compounds, MnO_2, etc. which liberate oxygen from H_2O_2 by purely catalytic action do not produce any chemiluminescence with lophine.

Thiebert and Pfeiffer[22] have found that many other iron complexes can be used instead of hemin. The best was salicylaldehyde-ethylenediimine ferrichloride (IX).



IX

A very interesting article appeared in 1937 by Specht[23] suggesting what is probably the first practical use of chemiluminescence. Specht suggests that a solution composed of luminol, H_2O_2, Na_2CO_3 and H_2O could be used for the detection and identification of blood stains in criminal investigations. A solution of the above ingredients can be applied in the dark with an atomizer to an area that

is suspected of being blood stained, and if any trace of blood is present a glow will be produced. This method is capable of detecting and identifying blood specks that are either too small or so changed in appearance as to be overlooked in an ordinary examination. The older the blood stains the better the method works.

Numerous tests showed that the following substances give no luminescence with this solution: saliva, urine, pus and other body secretions, milk, coffee spots, starch, organic or inorganic dyes, fabrics, leather, skin, fungus, oils, waxes, earth, stone, wood, metal rust, grass, or leaves.

Since Specht's article appeared two exceptions have been noted, namely certain samples of cinders, and the cores of cabbage and lettuce heads in the region of the cambium layer.

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Reported by R. B. Moffett
May 4, 1939

ACTION OF ORGANIC ACID CHLORIDES UPON ALIPHATIC ETHYLENIC HYDROCARBONS IN THE PRESENCE OF STANNIC CHLORIDE

Colonge and Mostafavi -- Ecole de Chimie Industrielle et Faculte des Sciences de Lyon

The addition of acid chlorides to the ethylenic double bond was reported by Kondakoff[2] a half-century ago. He pointed out the role of zinc chloride as a catalyst in the addition reaction between trimethylethylene and acetyl chloride to produce a β-chloroketone which could then lose one molecule of hydrogen chloride, leading to the formation of an α-unsaturated ketone. In 1898, Blanc[3] reacted acetyl chloride with 1,1,2-trimethylcyclopentene-2. He employed $AlCl_3$ as catalyst, thinking to apply the method of Friedel-Crafts to aliphatic hydrocarbons. Ten years later, Krapiwin[4] treated certain olefins with acetyl chloride or bromide in the presence of large amounts of aluminum bromide or chloride at a low temperature. He reported 20-40% yields of certain unsaturated ketones and observed the transitory formation of β-chloroketones. He stated that tetramethylethylene did not react with acid chlorides to produce ketonic products. According to him, the absence of a hydrogen atom on the carbon atom of the double bond prevents the normal reaction. Still later, Darzens[5] reported that cyclohexene adds acetyl chloride in the presence of certain metallic chlorides, of which stannic chloride is by far the most efficient catalyst. He extended the reaction to the homologs of acetyl chloride.

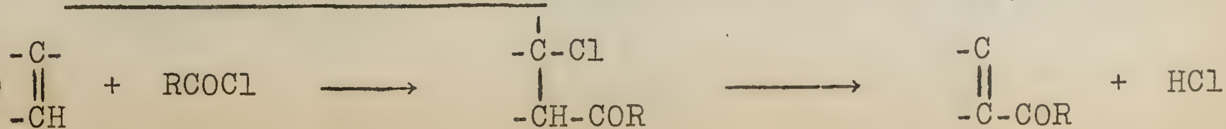
In the years since Darzens' work there have been numerous applications of this method which the authors call the Krapiwin-Darzens method. Most of these workers, thinking to apply the procedure of Friedel-Crafts in which $AlCl_3$ is more a reactant than a catalyst, used large quantities of the metallic chloride and worked at temperatures below 0°C.

In repeating the work of Kondakoff, the authors have shown that stannic chloride is a much more active catalyst for the reaction than is zinc chloride. Stannic chloride possess the added advantage of being soluble in organic acid chlorides and also in mixtures of olefins and acid chlorides.

Influence of Nature of Catalyst on Yield: The reaction was carried out with propionyl chloride and trimethylethylene in the presence of various metallic chlorides. The yields of unsaturated ketone follow:

Catalyst	Yield
$HgCl_2$	0%
$ZnCl_2$	16
$AlCl_3$	13
$TiCl_4$	40
$SnCl_4$	60

Mechanism of the Reaction: Two mechanisms may be postulated:

(1) 

$$(2)\quad \begin{array}{c}-C-\\ \|\\ -CH\end{array} + RCOCl \longrightarrow \begin{array}{c}-C-\\ \|\\ -C-COR\end{array} + HCl \longrightarrow \begin{array}{c}-C-Cl\\ |\\ -CH-COR\end{array}$$

Mechanism (1) is believed to represent the true picture of what occurs, because, contrary to Krapiwin's findings, the authors were able to add acetyl chloride to tetramethylethylene, obtaining a product which could be explained only by an initial addition.

<u>Constitution of Products</u>: An acid chloride may add to an unsymmetrical ethylenic hydrocarbon in two possible ways. Experimental results of this and of former investigations have proved that the chlorine atom fixes itself upon the more highly substituted carbon atom and the acyl radical upon the carbon atom carrying the hydrogen in compounds of the type $RR_1C{=}CHR_2$.

Although the addition of the acid chloride furnishes only a single β-chloroketone, the less of hydrogen chloride may, by contrast, yield either the α- or the β-unsaturated ketone. For example, 4,5-dimethyl-5-chlorohexanone-3 by losing hydrogen chloride may yield two different ketones:

$$CH_3-\overset{Cl}{\underset{CH_3}{C}}-\overset{H}{\underset{CH_3}{C}}-COCH_2CH_3 \quad \begin{array}{l}\nearrow\; CH_3-\overset{CH_3}{C}{=}\overset{CH_3}{C}-COCH_2CH_3\\ \searrow\; CH_2{=}\underset{CH_3}{C}-\underset{CH_3}{CH}-COCH_2CH_3\end{array}$$

Which isomer is obtained is determined by whether the hydrogen atom which is eliminated on losing hydrogen chloride is on the α- or on the γ-carbon atom with respect to the carbonyl group. It is generally accepted that the hydrogen on the α-carbon is the more mobile, although in some cases the two isomeric unsaturated ketones are formed simultaneously.

The simultaneous formation of the α- and β-unsaturated ketones by loss of hydrogen chloride from the β-chloroketone seems to depend upon the nature of the hydrocarbon chain. That is, whereas the products resulting from the addition of acid chlorides to trimethylethylene are always mixtures of the two forms, that formed when 2-methylpropene reacts with propionyl chloride is a pure compound, 5-methyl-4-hexene-3-one:

$$CH_3-\overset{CH_3}{C}{=}CH-COCH_2CH_3$$

One may deduce from the above that the presence of a hydrocarbon residue on the α-carbon with relation to the carbonyl group favors the formation of the β-unsaturated isomer along with the α-isomer.

<u>Experimental Results</u>: The following table gives the yields of unsaturated ketones after removal of HCl from the β-chloroketones:

Hydrocarbon	Acid chloride	Yield
Heptene-1	Acetyl	not det'd.
2-Methyl-1-propene	Propionyl	30%
2-Methyl-2-butene	Acetyl	53
" "	Propionyl	60
" "	Isobutyryl	40
" "	Pivaloyl	37

2-Methyl-2-butene	Diethyl acetyl	52
- " "	Benzoyl	40
2-Methyl-2-hexene	Acetyl	65
" "	Propionyl	50
2,3-Dimethyl-2-butene	Acetyl	30
1,2-Dichloroethylene	"	0
3-Chloro-1-propene	"	0

Influence of Structure of Reactants Upon Yield: Olefins of the type $RCH=CH_2$ react energetically with the acid chloride, but with the authors' technique it is impossible to isolate the ketone because it condenses with itself under the influence of the reactants.

More highly substituted olefins of the types $R_2C=CH_2$, $R_2C=CHR$, and $R_2C=CR_2$, do not give rise to the secondary reaction noted above as taking place with mono-substituted ethylenes.

The influence of the structure of the acid chloride on the yield of ketone appears to be rather feeble. In effect, for a given olefin, such as trimethylethylene, the yield of unsaturated ketone ranges between fifty and sixty per cent when the acid chloride is of the type RCH_2COCl. These yields are lowered to forty per cent when the acid chlorides are branched, as $R_2CHCOCl$ and $R_3C\text{-}COCl$.

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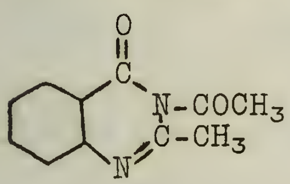
Reported by H. E. Conde
May 3, 1939

Fifty years ago D. Hooper discovered an alkaloid, vasicine, in the leaves of the Himalayan plant, "Adhatoda vasica (L.) Nees". Adhatoda is used widely in India as fish poison, insecticide, and for the relief of asthma. Peganine is obtained from the mother liquors resulting from the extraction of harmine and harmaline from the plant "Peganum harmala". It was proved to be the same as vasicine.

The compound has the following properties:

1. Formula, $C_{11}H_{12}ON_2$. M.P. 212°.
2. Monobasic and forms a methiodide.
3. $POCl_3$ replaces an OH with Cl to form chlorovasicine.
4. Zerewitinoff determination indicates one active hydrogen.
5. Acetic anhydride forms two acetyl derivatives.
6. $KMnO_4$ oxidizes it to an acid, the methyl ester of which gave anthranilic acid and glycine with NaOH. Spath suggested 4 possible structures for the methyl ester.



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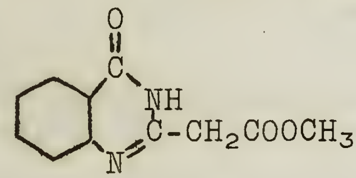

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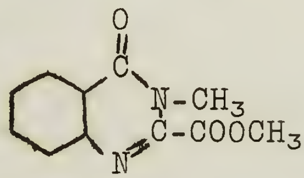
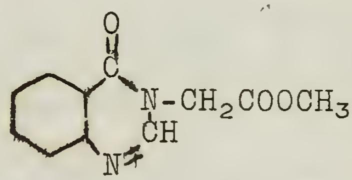
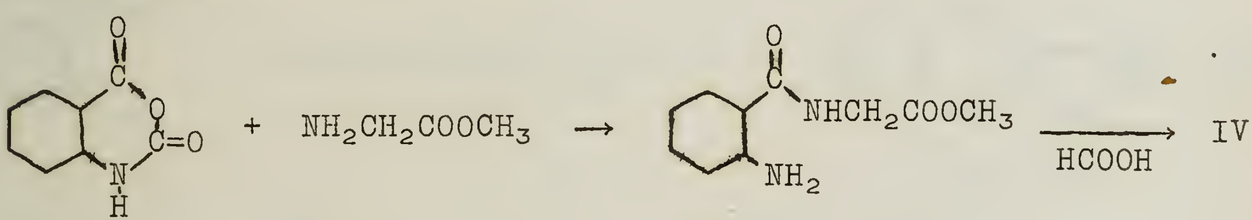


III

IV

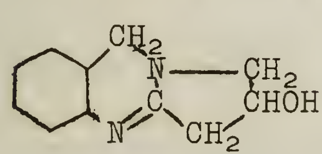


The acid was decarboxylated with Cu-bronze to give 3-methyl-4-keto-3,4-dihydroquinazoline, a compound already synthesized. Therefore it was given the structure IV. Spath also synthesized the acid as follows:

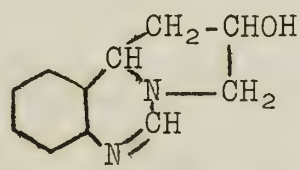


V VI

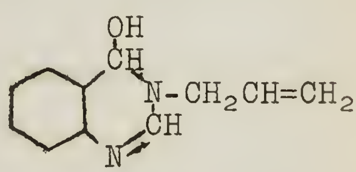
For the alkaloid Spath and Nikowitz suggested the following possible structures.



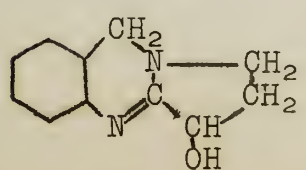
XVII



XVIII



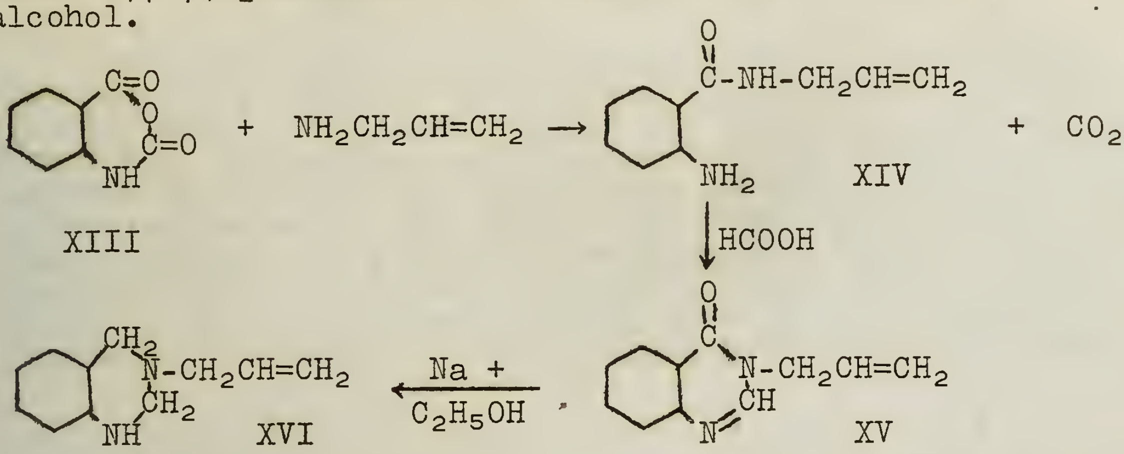
IX



X

XI XII

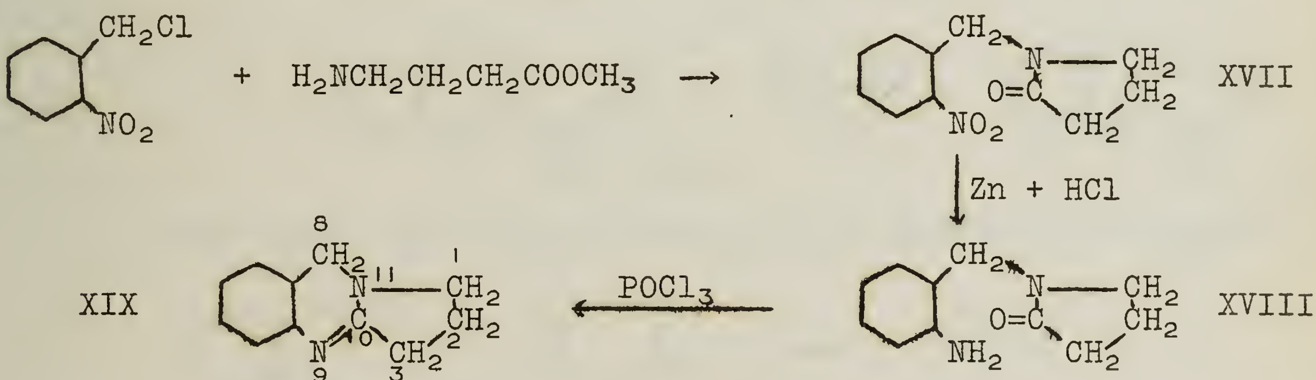
Spăth preferred IX but the fact that the alkaloid cannot be catalytically reduced questioned this structure. Hanford, Liang and Adams prepared compound XVI which was not identical with the compound $C_{11}H_{14}N_2$ obtained from vasicine with reduction by sodium and alcohol.



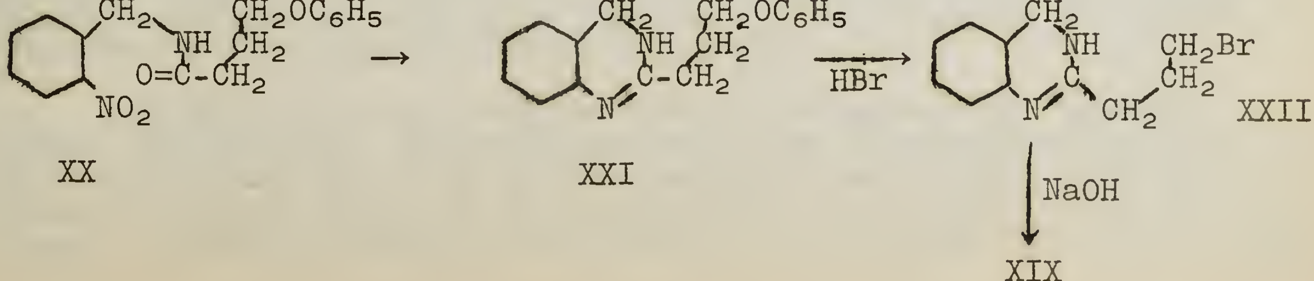
Reynolds and Robinson also synthesized IX by reacting allyl iodide with quinazoline and found it was not identical with peganine.

Two questions now arise: 1) Does peganine consist of a quinazoline ring with a side chain or a tricyclic ring system? 2) Is the oxygen in position 4 of the acid resulting from the $KMnO_4$ treatment originally present in peganine or does it appear with oxidation?

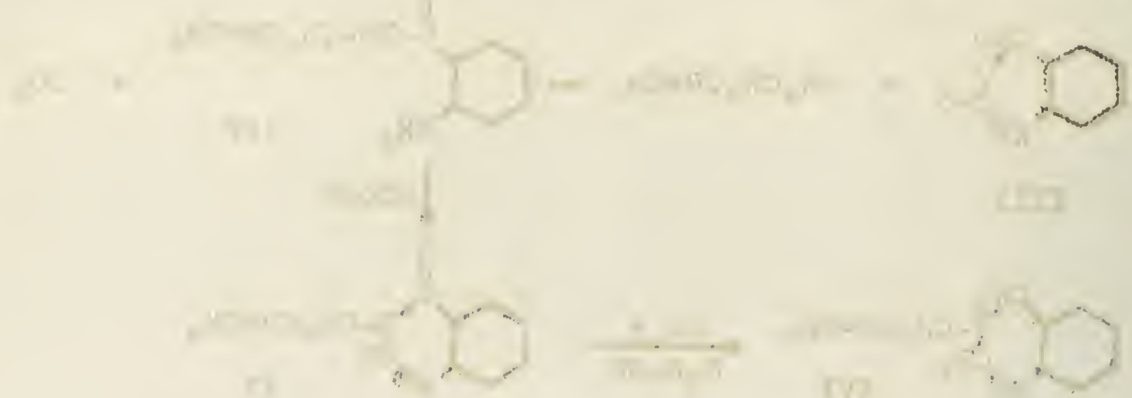
In order to prove whether a ring system was present desoxyvasicine (XIX) was prepared simultaneously by Hanford, Liang and Adams, and by Spăth, Kuffner and Platzer. Desoxyvasicine, pegene-9, is obtained from chlorovasicine with Zn + HAc. Spăth used the following synthetic procedure.



An outline of a second synthesis of XIX by Adams et al., and another by Spăth, is as follows:



[illegible] preferred IX [illegible] that the [illegible] should be [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]

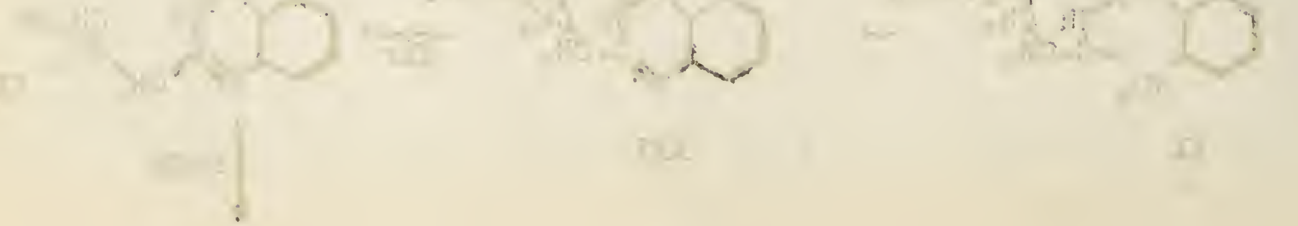


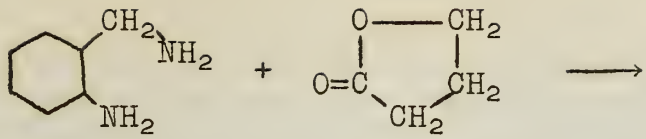
[illegible] XI [illegible] [illegible]

[illegible] [illegible] [illegible]

[illegible] [illegible] [illegible] [illegible] [illegible] following [illegible]

An outline of a [illegible] synthesis of XII by Adams et al., [illegible] by [illegible], is as follows:



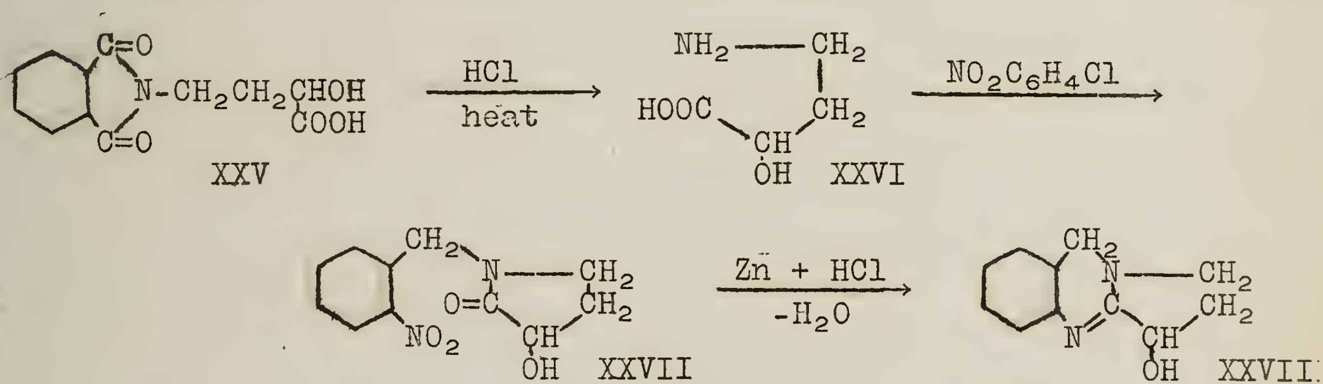
(Späth)  XIX

The final step in the determination of the structure of peganine was the placing of the hydroxyl group. To determine this, Morris, Hanford and Adams studied the derivative of vasicine obtained with H_2O_2. In proving the structure of this oxidation product desoxyvasicine was oxidized to XXIII whose structure was proved by a synthesis similar to that above. Phenoxybutyryl chloride reacted with o-aminobenzamide to yield the corresponding amide. The ring was closed by heat, the phenoxyl group replaced by Br with HBr, and finally a ring closure with alkali gave XXIII. When XXIII was treated with $Pb(Ac)_4$ followed by hydrolysis XXIV was obtained which

XXIII  XXIV

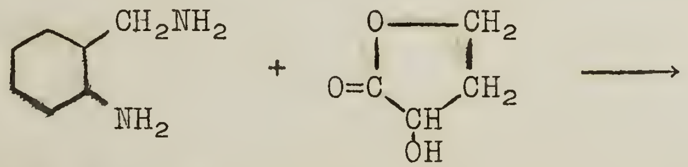
was identical with the oxidation product of vasicine, and the structure of vasicine was deduced as being XXVIII.

A synthesis of peganine by Späth cinched the correct structure:



XXV XXVI XXVII XXVIII

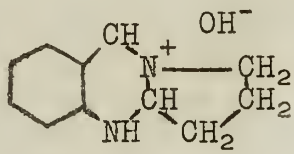
Later Späth gave the following simple synthesis of peganine:

 XXVIII

Späth resolved peganine by means of tartaric acid. With d-tartaric acid he isolated the l-form and from the mother liquors likewise the d-form with l-tartaric acid. He isolated the l-form of vasicine in the plant "Adhatoda vasicin".

Finally work has been done on the biogenesis of vasicine by Schöpf and Oechler. They imagined that the quinazoline ring resulted from the interaction of o-aminobenzaldehyde and α-hydroxy-γ-aminobutyric aldehyde followed by isomerization and shift of two hydrogen atoms. α-Hydroxy-γ-aminobutyraldehyde is not known but a synthesis

of desoxyvasicine by the use of γ-aminobutyraldehyde in the form of the diethylacetal makes the above hypothesis reasonable. The γ-aminobutyraldehyde condenses with o-aminobenzaldehyde to form the base XXIX in which under the action of palladium and hydrogen two hydrogen atoms shift to give desoxyvasicine.



XXIX

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Reported by J. Harkema
May 10, 1939

THE TAUTOMERISM OF p-HYDROXYAZO COMPOUNDS

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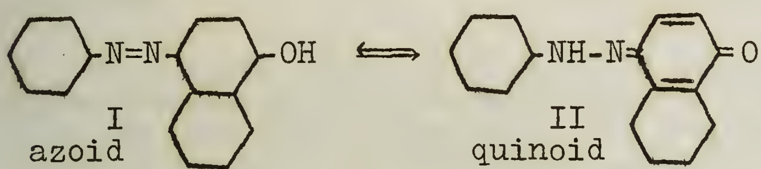
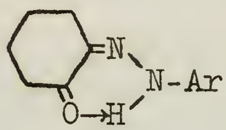
The introduction of a hydroxyl group into an aromatic azo compound gives rise to the possibility of tautomerism. Thus benzeneazo-α-naphthol may be transformed to the monophenylhydrazone of α-naphthoquinone, and this reaction would appear to be general. Although the hydroxyazo compounds have been studied from many aspects, until recently their constitution in many cases has not been satisfactorily established. The coupling reaction used in their preparation and the directing influence of the hydroxy group on bromination or nitration indicate the structure I, whereas condensation with hydrazine or addition of dienes appear to favor the structure II.



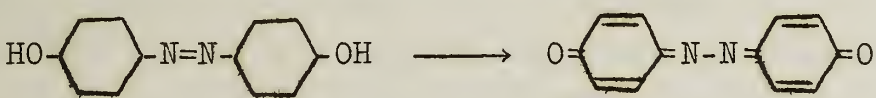
I azoid; II quinoid



III

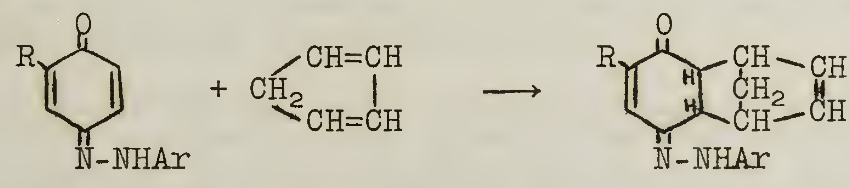
In the case of the o-hydroxyazo compounds most of the evidence indicates the hydrazone structure III (3a). The compounds are sluggish to alkali and phenylisocyanate; their absorption spectra support the quinoid structure (2). The evidence of infra-red absorption spectra (4) indicates hydrogen bridging and the chelate structure is preferred.

The case of the p-hydroxyazo compounds is not as clear cut. The oxidation of p,p'-dihydroxyazobenzene by silver oxide to the corresponding quinone azine indicates that it has the azoid structure (3a).



Many p-hydroxyazo compounds in contrast to the o- are alkali soluble and react with phenylisocyanate.

However, Lauer and Miller (6) using the Diels-Alder reaction showed that certain of them, such as 2,4-dinitrobenzeneazophenol, react as the quinone-hydrazone (at least two nitro groups in Ar were required).



(R = H, CH_3, Br)

Kuhn and Bär (5) concluded from their study of the absorption spectra of benzeneazo-α-naphthol that the reaction I ⇌ II took place depending on the solvent. The absorption spectrum in pyridine was different from that in acetic acid. Bergmann and Weizmann (1) confirmed Kuhn's conclusions on the basis of dielectric measurements of p-hydroxyazo compounds.

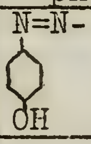
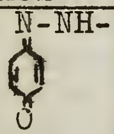
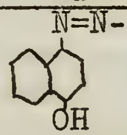
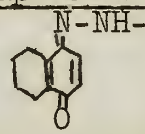
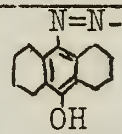
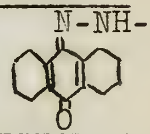
The body of this report will deal chiefly with the work of

Shingu (8), who has conducted extensive absorption spectra studies and has applied the electron and chromophore theories to their interpretation.

Benzeneazoanthranol:- This author prepared benzeneazoanthranol, to which on the basis of spectral and other evidence a quinone- monophenylhydrazone structure may be assigned. The benzeneazoanthranol made from anthranol and diazotized aniline is identical with the anthraquinone-monophenylhydrazone made through condensation of meso-dibromoanthrone and phenylhydrazine.

Methylation with dimethyl sulfate or methyl iodide and alkali yields the N-methyl derivative. Diazomethane fails to methylate. The benzeneazoanthranol is split by acids into anthraquinone and phenylhydrazine.

In respect to the stability of the azoid and quinoid structures, benzeneazo-α-naphthol is intermediate between p-hydroxyazobenzene, which has the azoid structure, and benzeneazoanthranol, which has the quinoid structure, a fact which parallels the stability of the keto forms of phenol, α-naphthol and anthranol. This is corroborated by a consideration of the difference between the azoid and hydrazone-quinoid total bond energies, as calculated according to Pauling (7).

Coupling component	phenol		α-naphthol		anthranol	
Approximate structural formula						
Difference of the total bond energies (azoid - quinoid)	-35 Cal		-6 Cal.		+23 Cal.	

The chief band of benzeneazoanthranol, occurring at 4500 Å, is unaltered by the solvent (pyridine favors the azoid and acetic acid the quinoid form). A comparison of the absorption band spectra of the N-methyl and O-acyl derivatives in Fig. 1 of known structure with the parent substance shows that the benzeneazoanthranol curve is analogous to that of the N-methyl derivative, and accordingly its structure may be formulated as quinoid. The displacement of the curve some 360 Å to the red may be attributed to the bathychromic effect of the substituent methyl. In contrast the O-benzoyl and O-acetyl derivatives have entirely different absorption curves.

Comparison of the influence of the solvent demonstrates (Fig. 2) the distinction between the two types of absorption bands. The absorption bands of the N-methylphenylhydrazone of anthraquinone and of the parent substance are displaced in a polar solvent such as alcohol toward the red, whereas those of the O-benzoyl derivative are shifted to the shorter waves.

Influence of substituents on the azoid-quinoid tautomerism:- In the terminology of Ingold and Robinson (3b) the influence of substituents on the azo-hydrazone tautomerism may be discussed on the basis of inductive and mesomeric effects according to the following electron shift scheme, which is analogous to the keto-enol tautomerism.

The so-called negative groups (terminology of Robinson) such as NO_2, COOH and halogens, have an electron pulling effect and the so-called positive groups such as CH_3, CH_3O, and NH_2, an electron repelling effect. Hence the latter will favor the azo structure and the former the hydrazone structure. The order in which various substituents favor the hydrazone structure in a compound such as benzeneazo-α-naphthol (where substitution occurs in the benzene ring) in general is according to the series:

o,p-NO_2 > o,p-COOH > m-NO_2, m-COOH ... m-X > o,p-X ...

m-OR > m-CH_3, (H) > o,p-CH_3 > o,p-OR

Benzeneazophenol derivatives:- The azoid structure of this compound is so stable that it is unchanged by any substituent.

Benzeneazoanthranol derivatives:- The introduction of a substituent favoring the azo structure does not alter in any way the quinoid structure of this molecule. Both the parent substance and its p-methoxy derivative have similar absorption spectra.

Benzeneazo-α-naphthol derivatives:- Not only substituents but also the solvent have marked influence on the constitution of this compound. Fig 3 shows two absorption bands in the visible (ethanol as solvent). Kuhn and Bär (5) have correlated the band of longer wave length (H-band) with the hydrazone and that of shorter wave length (A-band) with the azoid structure, which is confirmed by the absorption spectra of the derivatives. In Fig. 4 the curve for the p-methyl not only corresponds much more to that for the O-methyl than it does to that for the N-methyl derivative, but also to the curve for p-hydroxyazobenzene.

Introduction of the methyl group in the p-position strengthens the absorption band of shorter wave length (A-band) and weakens absorption at the H-band. The height of the H-band for the o-methyl derivative is lowest and for the m-derivative highest, and conversely the A-band is heightened in the order o > p > m.

A consideration of the effects of other substituents based on the absorption spectra of various benzeneazo-α-naphthol derivatives leads to the following summary. In alcohol as a solvent the hydrazone structure is favored according to the following order. The values given are for the ratio of the extinction coefficients of the two bands $\varepsilon H/\varepsilon A$, which may be taken as an approximation for the proportion of hydrazone-quinoid to the azoid form.

p-NO_2 >	o-COOH >	p-COOH >	o-NO_2 >	m-NO_2 >	m-Cl >	m-COOH >	o-CH_3O,
∞	∞	∞	2.3	1.9	1.5	1.15	0.9

m-CH_3O >	p-Cl >	p-Br >	o-C_2H_5O >	m-CH_3 >	(H) >	o-Cl >	p-CH_3 >
0.89	0.84	0.8	0.73	0.71	0.63	0.5	0.4

2,4,6-tribromo >	o-CH_3 >	p-CH_3O
0.3	0.23	0.22

In benzene as a solvent:

$\underline{o}$-C_2H_5O > $\underline{p}$-Br > (H) > $\underline{p}$-CH_3 > $\underline{p}$-CH_3O

Except for the special cases of $\underline{o}$-alkoxy and $\underline{o}$-halogen derivatives the conclusions based on the electron theory are confirmed.

Chromophoric considerations:- In general the auxochromic effect of substituents on the chromophoric groups considered (azoid and quinoid) differ for the unionized or homopolar form, and the ionized form or heteropolar anion.

The homopolar form is considered first. The chief band of $\underline{p}$-hydroxyazobenzene, analogous to the A-band above, is not markedly influenced by the introduction of a methyl group in the benzene nucleus, but a nitro group in the $\underline{p}$-position to the azoid group has a pronounced bathychromic effect, which is trivial for the $\underline{m}$- and $\underline{o}$-NO_2 compounds. This same auxochromic effect is noted in azobenzene, that is, the bathychromic effect of NO_2 is in the order $\underline{p} \gg \underline{o} > \underline{m} >$ (H) (Fig. 5).

In the case of a stable quinoid structure as found in benzeneazo-anthranol, the auxochromic effect of substituents is reversed. Positive groups as CH_3 and CH_3O have a bathychromic effect and the negative NO_2 group a hypsochromic effect in the order (H) > $\underline{o}$ > $\underline{p}$ > $\underline{m}$ in the bathychromic direction (Fig. 6).

The chromophoric evidence for the benzenazo-α-phenol derivatives is less satisfactory. In the case of the H-band, CH_3 and CH_3O groups in the $\underline{p}$-position have a bathychromic effect, and the NO_2 group a hypsochromic. For the A-band the CH_3 group has a hypsochromic and the halogens a considerable bathychromic effect. For this compound it is noteworthy that the same substituents which deviated from predictions based on electron theory have an anomalous auxochromic effect also, namely, the $\underline{o}$-alkoxy and $\underline{o}$-halogen derivatives.

Auxochromic effect of substituents in colored anions:- When a chromophoric homopolar compound is converted to a heteropolar through salt formation, an important color change takes place. The auxochromic groups work in a different manner on the ionized chromophore than on the homopolar form. For instance the NO_2 group has a bathychromic effect on the heteropolar form of benzeneazo-α-naphthol in the order $\underline{p} \gg \underline{o} > \underline{m} >$(H). The effects of various substituents on the colored anions may be summarized as follows:

1. In the $\underline{p}$-position a bathychromic influence is evidenced in an order which corresponds to the so-called negativity, but this is not true for the $\underline{m}$- and $\underline{o}$-positions.

$\underline{p}$-NO_2 > COOH > Cl > Br > (H) > CH_3 > CH_3O

2. The auxochromic effect depends on the position as follows:

R	bathychromic	hyperchromic
NO_2	$\underline{p} \gg \underline{o} > \underline{m} >$ (H)	$\underline{p} > \underline{m} > \underline{o}, >$ (H)
COOH	$\underline{p} \gg$ (H) > o,m	$\underline{o} > \underline{p} > \underline{m} >$ (H)
Cl	$\underline{p} > \underline{m} > \underline{o} >$ (H)	$\underline{p} > \underline{m} > \underline{o} >$ (H)
CH_3	(H) > $\underline{p}$,m > $\underline{o}$	m > (H) > $\underline{p} > \underline{o}$
CH_3O	o > m, (H) > p	(H) > $\underline{o}$,$\underline{m}$ > $\underline{p}$

3. Bathychromic influence has the following order:

2,4-dinitro > p-NO_2 > o-NO_2 > m-NO_2 > p-Cl > m-Cl > p-COOH > o-Cl > p-Br > o-CH_3O > m-CH_3O, o-C_2H_5O > (H) > p-CH_3 > m-CH_3 > o-,m-COOH > p-CH_3O > 2,4,6-tribromo > o-CH_3.

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Reported by S. J. Circle
May 17, 1939

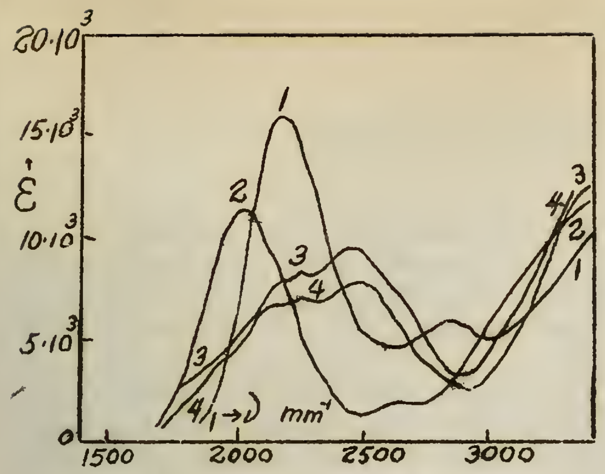


Fig.1. 1.Benzeneazoanthranol.
2.N-methyl derivative.
3. O-benzoyl derivative.
4. O-acetyl derivative.
(all in alcohol)

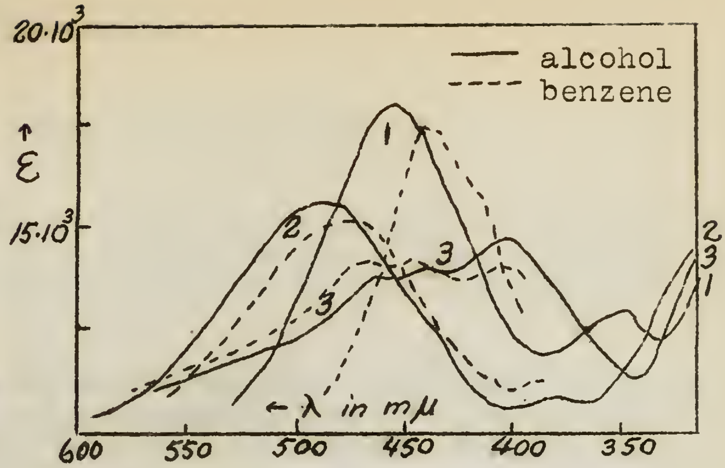


Fig.2. 1.Benzeneazoanthranol.
2.N-methyl derivative.
3.O-benzoyl derivative.

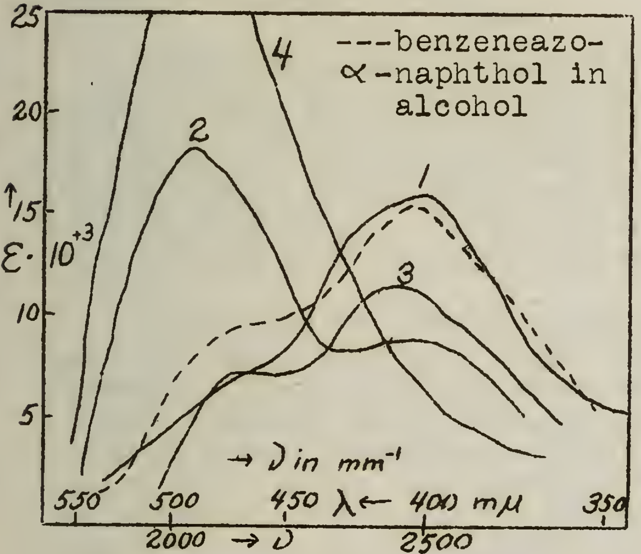


Fig.3. p-methyl benzeneazo-α-naphthol in various solvents.
1.alcohol 2. acetic acid
3. benzene 4. alcohol-KOH

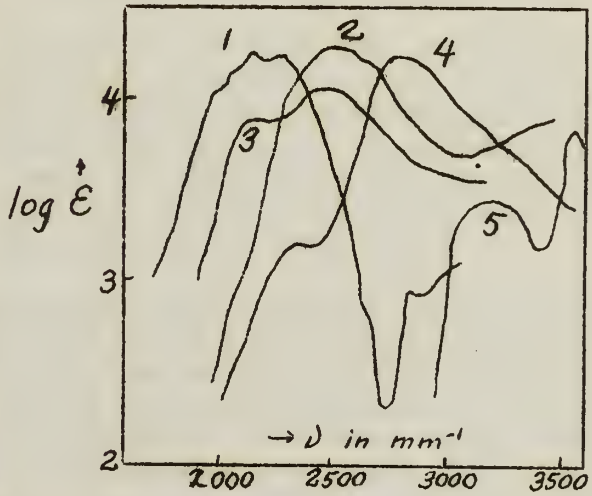


Fig.4. 1.N-methyl benzeneazo-α-naphthol (in benzene).
2.O-methyl derivative in benzene.
3.p-methyl derivative in benzene.
4.Benzeneazophenol in alcohol.
5.β-naphthol in hexane.

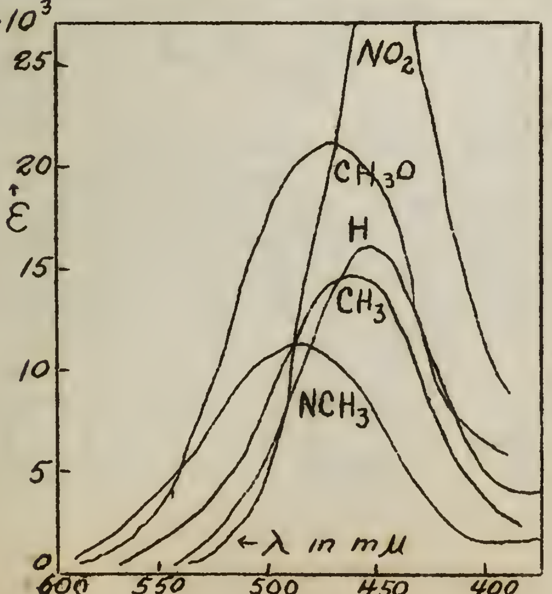


Fig.5. p-derivatives and the N-methyl derivative of benzene-azoanthranol (in alcohol).

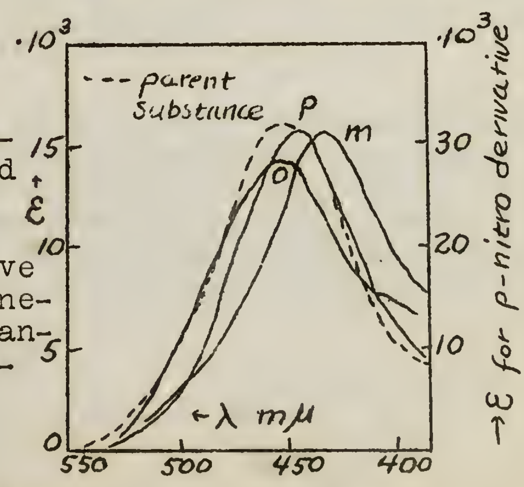
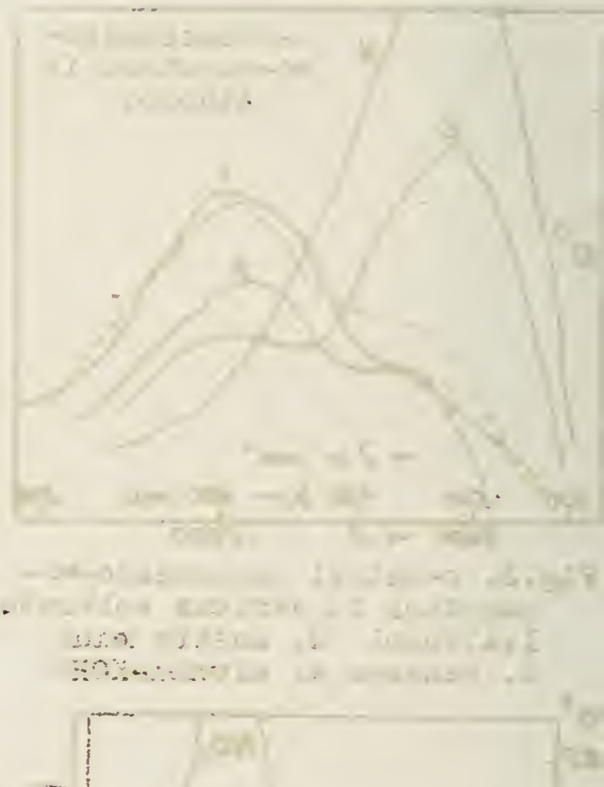
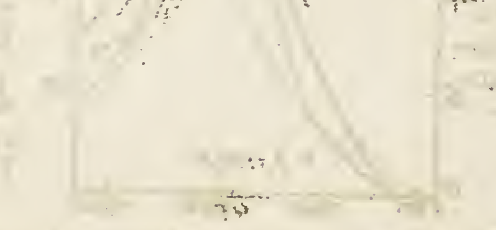


Fig.6. The three isomeric anthraquinone-momonitrophenylhydrazones (in alcohol).

S.Y.C.





Mannich -- Pharm. Inst. Univ. of Berlin

Shäfer and Tollens (1) obtained from the reaction of acetophenone, formaldehyde, and ammonium chloride a base to which they assigned the formula $(C_6H_5COCH_2CH_2)_3N$. Steam distillation of the hydrochloride of the base split off vinyl phenyl ketone.

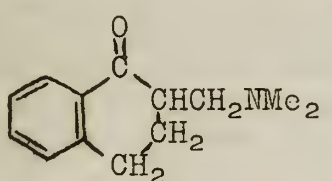
Mannich and coworkers (2) repeated the same experiment several years later and found the particular condensation to be more complicated than indicated by Shäfer and Tollens. Meanwhile, Mannich had successfully applied the reaction to a variety of ketones and amines.

A typical general equation demonstrating the preparation of β-keto bases follows:

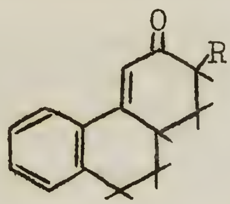
$$RCOCH_2R' + HCHO + R_2''NH_2^+Cl^- \longrightarrow RCOCHR'CH_2NR_2''H^+Cl^- + H_2O$$

Aliphatic β-keto bases were obtained through the reaction of aliphatic ketones with formaldehyde and ammonium salts, or more readily, from the hydrochloride of methyl amine or dimethyl amine (3). For example, these three amines gave with acetone, respectively, $(CH_3COCH_2CH_2)_3N$ (isolated as the oxime); $(CH_3COCH_2CH_2)_2NCH_3$; and $CH_3COCH_2CH_2N(CH_3)_2$. Other less readily defined products were formed when the salts of ammonia and methyl amine were employed.

It was found that acyclic ketones also condense with formaldehyde and amine salts to form the expected β-keto bases (4). Cyclohexanone yielded stable salts which decomposed at their melting points to the original amine salt and 2-methylenecyclohexanone. α-Tetralone under the same conditions produced compound I, which, after conversion to the free amine, was reduced to the hydroxy compound which could be benzoylated. It could be dehydrated to the dihydro compound and then reduced to 1,2,3,4-tetrahydro-3-(dimethylaminomethyl)naphthalene.



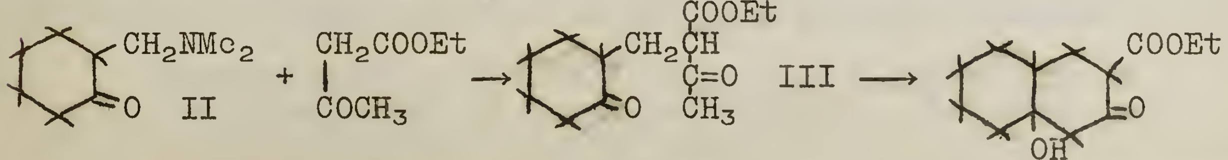
I



V R = H

Va R = CH_3

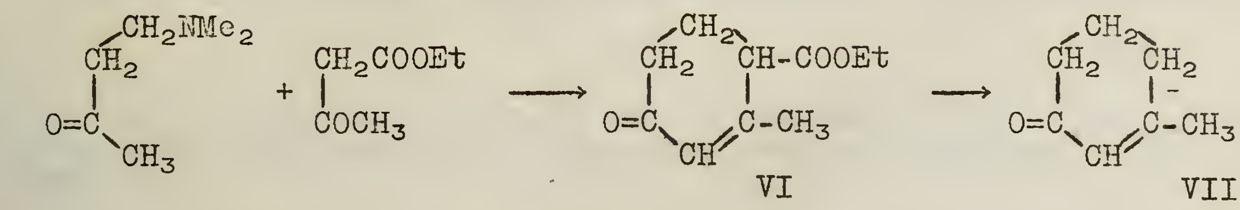
Acetoacetic ester was condensed with 1-(dimethylaminomethyl)-2-cyclohexanone, II (5). 2-Methylenecyclohexanone was probably formed primarily, thus explaining the reaction of acetoacetic ester; and, since compound IV and not III was isolated, ring closure had evidently taken place. Substitution of compound I for II gave compounds V and Va when acetoacetic ester and methyl acetoacetic ester, respectively, were used.



IV

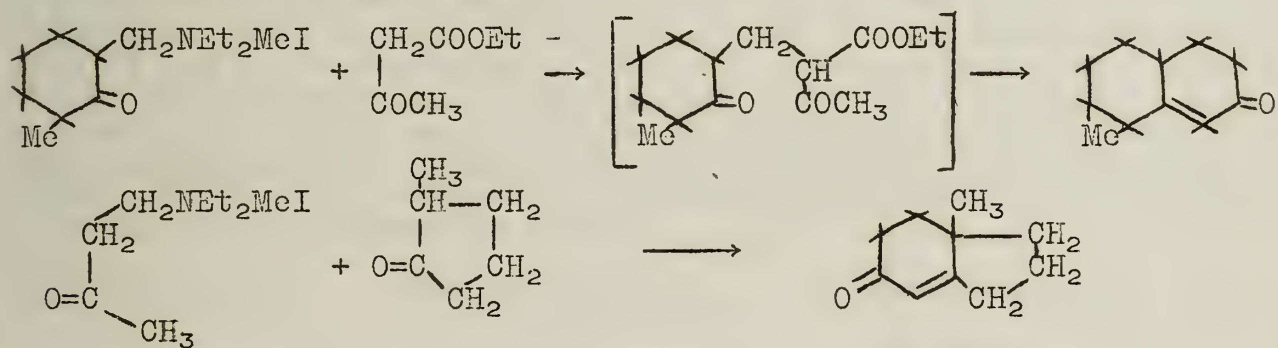
Mannich (6) carried out the same condensation with the replace-

ment of II by 1-dimethylamino-3-butanone. Compound VI was obtained along with some of VII, but boiling VI with dilute sulfuric acid converted it to VII.



Repetition of this reaction, using malonic ester instead of acetoacetic ester, provided a satisfacroty yield of the expected diethyl 3-ketobutylmalonate, which on further treatment with sodium ethoxide gave dihydroresorcinol through inner condensation and loss of a carbethoxy group.

Robinson (7) has been studying syntheses of substances related to sterols. He and his associates synthesized certain octalones and ketotetrahydrohydrindenes which are of the angular methyl substituted type. In most of his work quaternary ammonium salts prepared by Mannich's reaction were used as a source of the ketones. The following equations illustrate these results:



A large number of β-keto bases have been prepared from aliphatic-aromatic ketones, formaldehyde, and secondary amines, as both the ketone and amine were varied widely (8). Acetophenone, for example, reacted with formaldehyde and dimethyl amine, afforded ω-dimethylamine hydrochloride in good yields, according to the equation:

$$C_6H_5COCH_3 \;+\; HCHO \;+\; (CH_3)_2NH_2^+Cl^- \;\longrightarrow\; C_6H_5COCH_2CH_2N(CH_3)_2H^+Cl^- \quad \text{VIII}$$

Aqueous solutions on boiling decomposed to give the simple amine hydrochloride and the α,β-unsaturated ketone. Superheated steam or dry distillation <u>in vacuo</u> produced the same effect. In the case of vinyl phenyl ketones, the yields of the unsaturated ketone were decreased due to polymerization. Reduction of the unsaturated ketones actually afforded a means of methylating aromatic-aliphatic ketones. For example, propioanisone was prepared from p-methoxyacetophenone.

Compounds such as $C_6H_5COCH_2CH_2NC_5H_{10}$, β-piperidinoethyl phenyl ketone, were described as local anesthetics. Reduction of the free β-keto bases to β-amino alcohols caused a loss of anesthetic properties but the benzoylated alcohol produced marked anesthesia.

Reichert (9) used the method of Mannich for the preparation of 1,3-amino ketones. With these he condensed nitromethane, and, in the case of ω-dimethylaminopropiophenone (IX), three products were identified (X,XI,XII).

$C_6H_5COCH_2CH_2CH_2NO_2$ $(C_6H_5COCH_2CH_2)_2CHNO_2$ $(C_6H_5COCH_2CH_2)_3CNO_2$

X   XI   XII

It is of interest to note that substances of the type $C_6H_5C{\equiv}CH$ react with formaldehyde and secondary amines, according to the equation (10):

$$C_6H_5C{\equiv}CH \;+\; HCHO \;+\; HNR_2 \;\longrightarrow\; \underset{\text{XIII}}{C_6H_5C{\equiv}C\text{-}CH_2NR_2} \;+\; H_2O$$

The 1-phenyl-3-dialkylamino-1-propyne (XIII) was obtained in good yields. Reduction gave the corresponding propane. Addition of cold dilute sulfuric acid to XIII produced IX, which is the same amine as VIII.

Recently, Mannich (11) treated β-keto amines with formaldehyde in order to obtain aminohydroxy ketones and aminopolyhydroxy ketones. To avoid complications which can arise through the reaction of formaldehyde with a primary or secondary amino group, amino ketones with a tertiary nitrogen were employed. From the condensation of 1-dimethyl-3-butanone (XIV) with formaldehyde, a part of XIV was recovered along with XV and a basic mixture which could not be cleared up. But, when the reaction mixture was acidified and reduced, a mixture of bases was isolated, which, upon fractional distillation, gave some recovered XIV, compound XVI, a mixture of liquid diastereoisomeric dihydroxy bases (XVII), and a mixture of trihydroxy compounds, one of which probably has the structure XVIII.

$CH_3COCH_2CH_2NMe_2$ (XIV) $CH_3COCH(CH_2NMe_2)_2$ (XV) $CH_3\overset{OH}{C}HCH(CH_2NMe_2)_2$ XVI

$CH_3\overset{OH}{C}H\text{-}\overset{CH_2OH}{C}HCH_2NMe_2$ XVII

$HOCH_2CH_2\overset{OH}{C}H\text{-}\overset{CH_2OH}{C}HCH_2NMe_2$ XVIII

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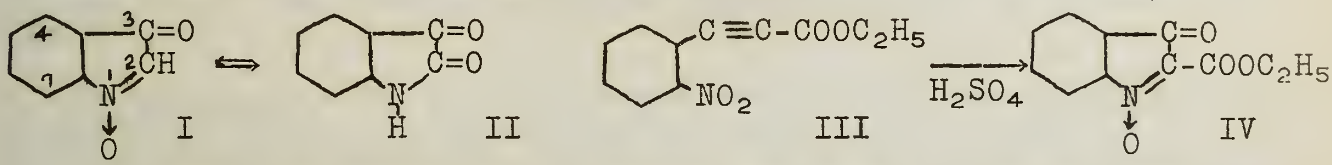
Reported by J. H. Burckhalter
May 17, 1939

ISATOGENS AND ISO-ISATOGENS

Ruggli -- University of Basel, Switzerland

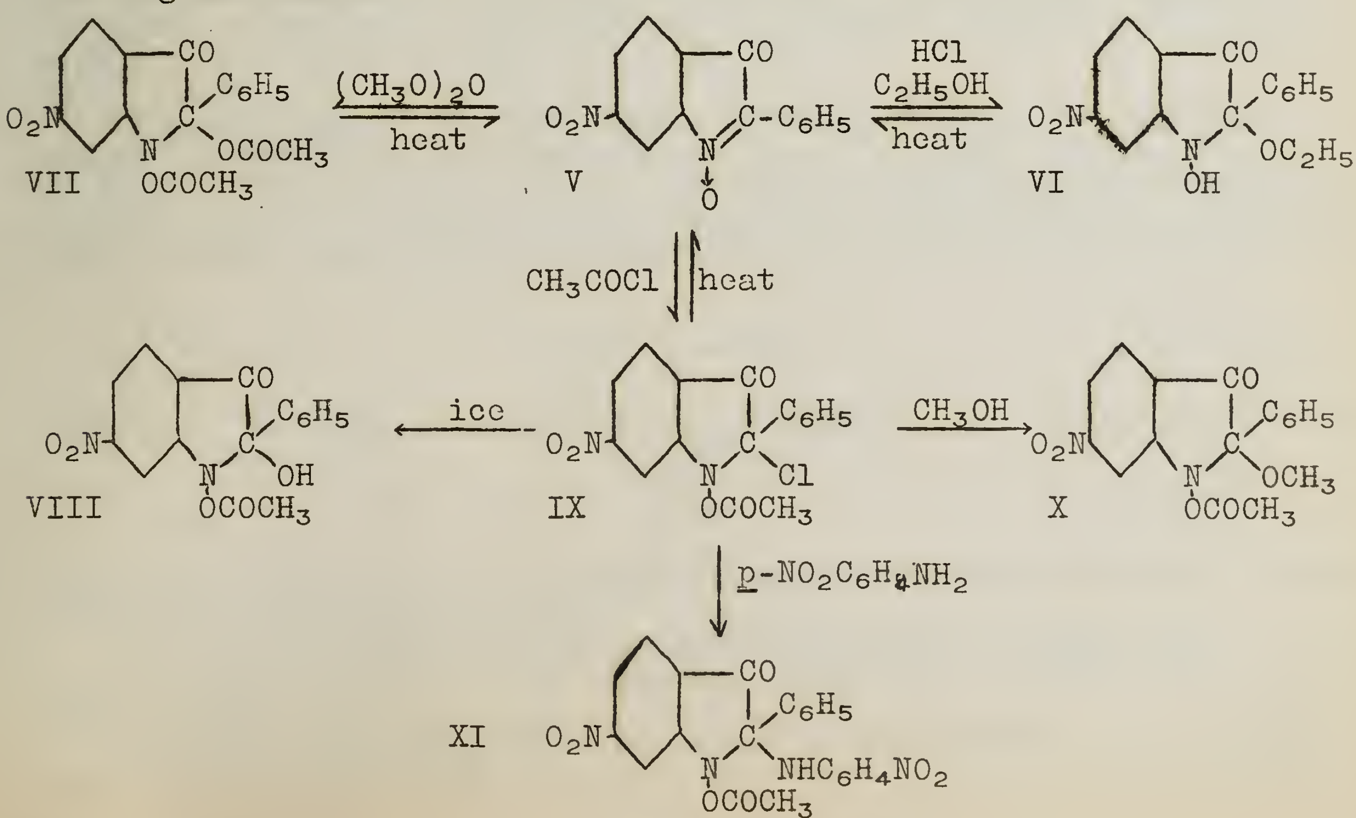
In 1882 A. von Baeyer in his work on the structure of indigo discovered and named the first isatogen which was the ethyl ester of isatogenic acid (IV). P. Pfeiffer discovered a simple synthesis for isatogens and prepared a large number of these compounds. The simplest member in this class, isatogen (I), is unknown. It is isomeric with isatin (II) and possibly an equilibrium exists between the two, with the equilibrium displaced far to the right.



I II III IV

<u>Structure and Reactions of Isatogens</u>:- When isatogens are treated with zinc and acetic acid they are converted into indoxyls. From this it was concluded that they were cyclic compounds. They contain two reactive groups, a carbonyl group and the nitrone grouping $=N\rightarrow O$. When isatogens react with hydroxylamine some oxime formation takes place on the carbonyl group and some on the nitrone group. Pfeiffer pointed out that the isatogens were the first definitely known <u>meta-quinoid</u> compounds. It has been possible to form the quinhydrone analogue by adding phenylindoxyl (the hydroquinone analogue) to phenylisatogen (the quinone analogue). In this way a highly colored substance (phenylisatogen) and an almost colorless substance (phenylindoxyl) form a black crystalline compound which is easily separated into its components.

The addition reactions of the isatogens can most easily be shown by means of a diagram using 6-nitro-2-phenylisatogen (V) as the starting material.



The addition of acetyl chloride to V yields IX. This compound is very reactive. With traces of water it forms isatogen. It reacts with methyl alcohol to give compound X and with p-nitroaniline to give compound XI. With a more basic compound the isatogen V is formed immediately. The ether acetates cannot be made by the direct addition of the alkyl acetates to the nitrone. It is interesting to note that no carbonyl group could be detected in compound VII nor in XI.

L. I. Smith points out that most of the reactions of isatogens which have been studied in detail can be interpreted logically as 1,3-addition. There is also a conjugated system in the quinoid structure of the isatogens: $O=C-C=N \rightarrow O$. This would be capable of 1,5-addition. The further study of these compounds should be very interesting.

Preparation:- The first isatogen was made by the action of H_2SO_4 on the ethyl ester of o-nitropropiolic acid (III) to give IV.

Pfeiffers's synthesis consisted of exposing a pyridine solution of the halogen derivatives of o-nitrostilbene or o-nitrotolanes to sunlight.

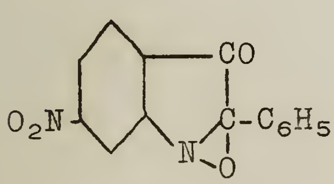
Recently Ruggli found a new method for the preparation of isatogens. He dissolved the o-nitrotolanes in chloroform using nitrosobenzene as a catalyst. He allowed the mixture to stand for 19 days and obtained a very pure product in 59% yield.

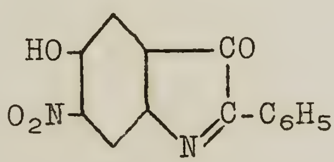
Ruggli's latest synthesis consists in reducing o-nitrobenzil with Raney nickel. He found that a solution of o-nitrobenzil readily absorbed four atoms of hydrogen. If he stopped the reaction at this point he obtained a 34% yield of 2-phenylisatogen.

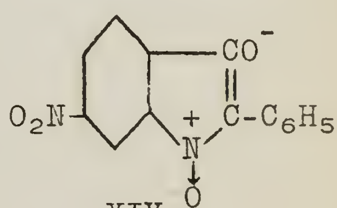
Mechanism of Isatogen Formation:- All that can be definitely said about the formation of isatogens is that in Pfeiffer's method three steps are involved: 1) HX is eliminated from the halogenated stilbene, 2) the oxygen migrates to the carbon; 3) the ring closes.

It has been definitely shown that only the o-nitrotolanes form isatogens. Pyridine, and quinoline to a lesser degree, seem to be specific catalysts for this ring closure.

Iso-isatogen:- In 1919 Ruggli found that when the deep red 6-nitro-2-phenylisatogen was treated with alcoholic HCl there was obtained a light yellow isomer. To this he tentatively assigned the structure XII. Recently he has studied the formation of an analogous isomer from 2-phenyl-6-carbethoxyisatogen using alcoholic H_2SO_4.


XII


XIII


XIV

Ruggli gave the name iso-isatogen to these compounds which are isomeric with the quinoid structure.

The iso-isatogens differ from the isatogens in many ways.

1. They do not show any phenolic properties and hence structure XIII is ruled out.

2. They are practically insoluble in water which rules out the salt-like structure XIV.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

3. They form only one oxime whereas the quinoid isatogen forms two oximes (the C- and the N-oxime).

4. They react with phenylhydrazine to give compound XV while the isatogens are reduced to indoxyls.

5. They do not form quinhydrones with the corresponding indoxyls.

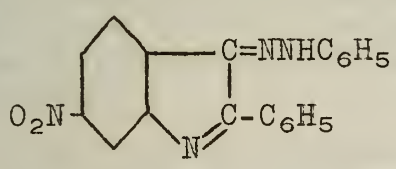
6. They do not liberate iodine from a solution of KI in acetone while the quinoid form does.

7. They have the same composition and the same molecular weight as the isatogen from which they are formed.

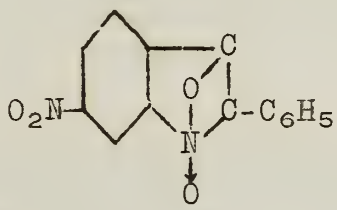
8. On stereochemical considerations XVI can be ruled out.

9. When iso-isatogen is heated above its melting point in acetic acid for five minutes it rearranges to the quinoid structure.

The evidence presented above shows that all obvious structures for the iso-isatogens, other than the three-membered ring, must be abandoned since they conflict with some of the experimental data.



XV



XVI

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Reported by F. C. Dietz
May 24, 1939

MECHANISM OF KETONE FORMATION FROM CARBOXYLIC ACIDS

Neunhoeffer and Paschke -- Breslau

The formation of ketones from carboxylic acids or their salts by thermal decomposition has been surmised to take place in various ways:

1. $(CH_3COO)_2Ca \longrightarrow CH_3COCH_3 + CaCO_3$

2. $(CH_3COO)_2Ca \longrightarrow CaO + (CH_3CO)_2O \longrightarrow CH_3COCH_3 + CO_2$

3. $(CH_3COO)_2Mg \longrightarrow CH_3COCH_3 + MgO + CO_2$

4. $HOOC(CH_2)_4COOH \xrightarrow[Ba(OH)_2]{Fe} (CH_2)_4 \left\langle \begin{matrix} COO \\ COO \end{matrix} \right\rangle Fe \longrightarrow (CH_2)_2 \left\langle \begin{matrix} CH_2 \\ CH_2 \end{matrix} \right\rangle C{=}O + FeC($

It can be said in general that acids with basic catalysts or salts of acids form intermediate salts which decompose into ketones and metal oxide or carbonate depending upon the basicity of the oxide. Catalytic transformations, those involving carboxylic acids and basic catalysts, take place at lower temperatures and give better yields than acid or salt thermal decompositions. The difference would lie in the reaction mechanism.

Only salts of carboxylic acids which have a hydrogen atom alpha to the carboxyl group can give ketones upon thermal decomposition. Calcium trimethylacetate yields no hexamethylacetone. Farmer and Kracovski have obtained no cyclic ketone from $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid. Diisopropyl ketone was obtained from calcium isobutyrate

To account for the above facts a two-step mechanism for the decomposition was proposed and shown to be correct.

1. Acid or salt $\longrightarrow$ β-keto acid or salt

   $(CH_3COO)_2Ca \longrightarrow CH_3COCH_2COO\text{-}CaOH$

2. Decarboxylation

   $CH_3COCH_2COO\text{-}CaOH \longrightarrow CH_3COCH_3 + CO_2 + CaO$

There might be some doubt as to the application of this mechanism to the formation of many-membered cyclic ketones. Ruzicka has assumed that an intramolecular reaction leads directly to the cyclic ketone. The fact that monocyclic ketones have been obtained by the thermal decomposition of dibasic acids and their anhydrides weakens the claim that the metal ion in the case of salts, thorium for example, tends to bring into close approach the ends of long chains so that closure can take place.

Carothers, basing his conclusions on analogous reactions of his polyanhydrides and polyesters, has claimed that by the thermal decomposition of a salt a linear polyketone is first produced which separates into simple ketones.

$$\text{-R-CO-R-CO-R-CO-R-CO-R-CO-} \longrightarrow \text{R C=O}$$

[illegible] OF KETONES FROM CARBOXYLIC ACIDS

[illegible] -- [illegible]

The preparation of ketones from carboxylic acids or their salts by thermal decomposition [illegible]

1. $(CH_3COO)_2Ca \longrightarrow CH_3COCH_3 + CaCO_3$

2. [illegible]

3. [illegible]

4. [illegible]

[illegible]

[illegible]

[illegible]

1. [illegible] acid $\longrightarrow$ β-keto acid [illegible]

[illegible]

2. Decarboxylation

[illegible] $\longrightarrow$ [illegible] $+ CO_2$

[illegible]

[illegible]

[illegible]

To support his claim he presented as evidence the thermal decomposition of thorium octadecanedioate; first was produced a white solid polymeric ketone of consistent formula which upon molecular distillation was transformed into cycloheptadecanone. No mechanism was suggested to account for the breaking of the linkages in the chain; it was also thought unlikely a cyclic ketone would polymerize to a polyketone.

The proposed intermediate basic β-keto salt of Neunhoeffer could undergo enolization and loss of water to give a salt incapable of forming a ketone unless acted upon by water or acid.

$$1.\quad CH_3COCH_2COO\text{-}CaOH \xrightarrow{-H_2O} \begin{array}{l} CH_3CH\text{-}CH_2\text{-}C{=}O \\ \quad\;\; | \qquad\quad\;\; | \\ \quad\;\; O\text{—}Ca\text{—}O \end{array}$$

The reversal of this proposed reaction would account for better ketone yields in the presence of excess acid and steam. Work by Vavon and Apiche, Vogel, and Ardagh support this. Evidence for the two-step mechanism follows:

2. Ba adipate (dried 110°) $\xrightarrow{290\text{-}430^\circ}$ cyclopentanone (85%)

3. Ba adipate (very dry) $\xrightarrow{430^\circ}$ cyclopentene + some cyclopentanone + $BaCO_3$ + C (residue)

4. Ba adipate / Adipic acid $\xrightarrow{260^\circ}$ cyclopentanone + H_2O / Pure $BaCO_3$ residue

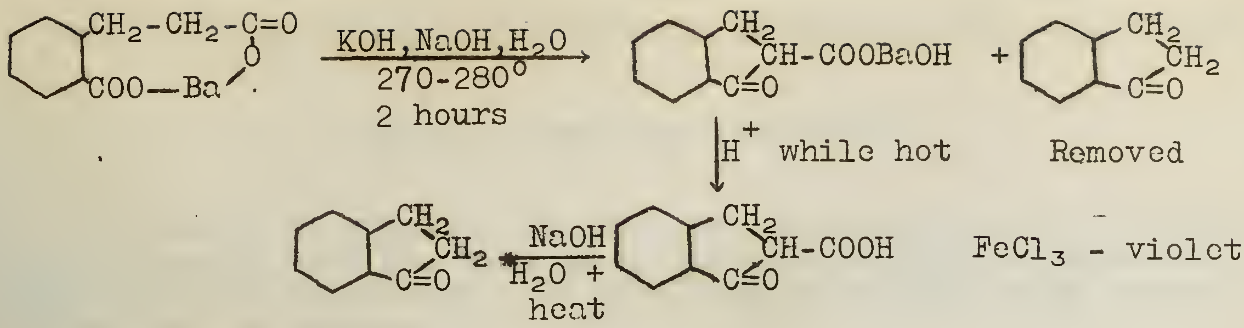
5. Ba adipate + BaO $\xrightarrow{375^\circ}$ cyclopentene (41%); 47% C in residue

Note that basic conditions lower the reaction temperature and favor the formation of side products.

$$6.\quad \begin{array}{l} CH_2\text{-}C{=}O \\ |\qquad\;\; \backslash \\ |\qquad\quad CH\text{-}COO\cdot\frac{Ba}{2} \\ |\qquad\;\; / \\ CH_2\text{-}CH_2 \end{array} \longrightarrow \text{cyclopentene; } BaCO_3 \text{ residue + C}$$

This reaction corresponds to reaction 5 where the BaO favors a supposed reaction 1 unfavorable to ketone formation.

Since it was found impratical to isolate from the decomposition of barium adipate salts of cyclopentanone-o-carboxylic acid. detection was done by color comparisons. Small amounts of barium adipate with BaO in small flasks were heated in a copper block for 1.5 minutes to 450°. After being made acid, ferric chloride was added to produce a green color: blue from the reaction with cyclopentanone-o-carboxylic acid and yellow from excess ferric chloride. Fully agreeing color shades appeared when synthetic barium cyclopentanone-o-carboxylate was treated similarly. The barium salt of phenylpropionic-o-carboxylic acid gave an excellent ferric chloride raction. Also by means of favorable basic conditions the intermediate β-keto acid formation was shown.



It was shown that under suitable conditions basic constituents of salts could be dispensed with. The monoethyl ester of adipic acid was transformed by thermal decomposition into the ethyl ester of cyclopentanone-o-carboxylic acid. Adipic acid distilled from Jena glass and quartz gave quantitative yields of cyclopentanone. Phenylpropionic-o-carboxylic acid gave α-hydrindone almost quantitatively at 300°. Sebacic and azelaic acids gave as low yields of cyclic ketones as the salts did. In the case of acetic acid basic catalysts and high temperature formed the yields. The yield of acetone varied with temperature from 1% at 290° to 12% at 340°. Above 340° the yields fell off.

It was indicated that the formation of β-keto acids and their salts by the thermal decomposition of carboxylic acids or their salts is a reversible reaction. The decarboxylation of β-keto acids could be expected to be an equilibrium reaction in which the equilibrium has been shifted far toward decarboxylation. Acetic acid was obtained from acetone, steam and CO_2 by heating for several days at 350°. Adipic acid was prepared from cyclopentanone, water and CO_2 by heating at 330° for a day. The reversibility of the thermal decomposition reaction was indicated.

To summarize, the mechanism of ketone formation from carboxylic acids involves the formation of a β-keto acid and subsequent decarboxylation. Basic catalysts are not entirely necessary for the transformation to proceed and the reactions are reversible.

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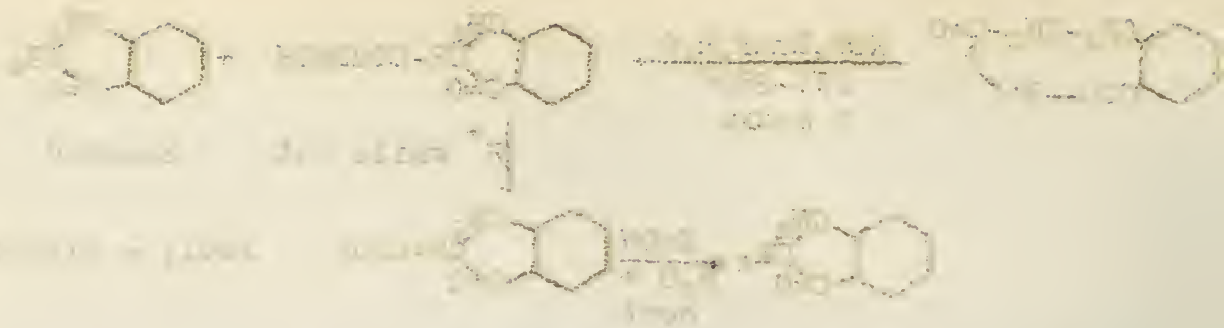
Reported by J. F. McPherson
May 24, 1939



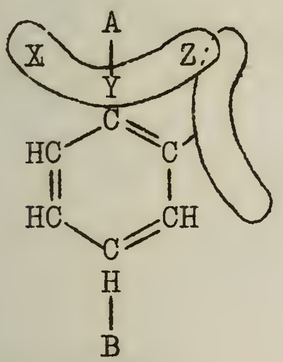
MOLECULAR DISSYMMETRY DUE TO RESTRICTED ROTATION

IN THE BENZENE SERIES: AN OPTICALLY ACTIVE ETHYLENIC DERIVATIVE

Mills -- Cambridge University

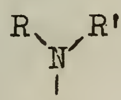
Molecular dissymmetry arising from the restriction of rotation about a single bond has been shown to occur in *peri*-substitution derivatives of naphthalene (1) and later in certain *ortho* substituted derivatives of benzene (2).

The derivatives of naphthalene and benzene in which this effect was demonstrated contained a grouping XYZ which could rotate about the axis AB when the adjacent positions (*o*- or *peri*-) were occupied by hydrogen atoms but was confined between more or less narrow limits of rotation when a large substituent, such as $-SO_3^-$ or $-N(CH_3)_3^+$ was introduced into one of these positions.



The types of structure most obviously suitable for the rotating complex are the substituted amino group I and the substituted vinyl group II.

The compound III was prepared by Mills and Kelham (2) and resolved with active brucine. The brucine salt showed mutarotation in chloroform solution. In this case $-NCH_3(Ac)$ is the rotating group and $-SO_3H$ the obstructing group. Apparently the grouping $-COOCH_3$ is not large enough to cause restricted rotation since the analogous compound IV could not be resolved.



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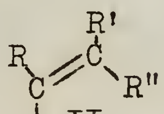
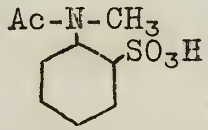
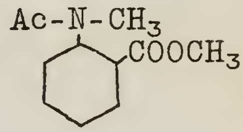


II

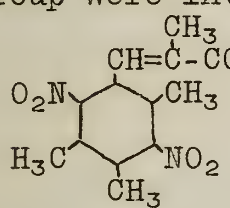


III

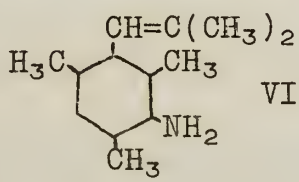


IV

The compounds V, VI and VII which contain a substituted vinyl group were investigated (3). They were found to be non-resolvable,



V



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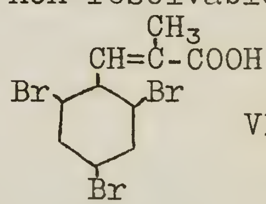


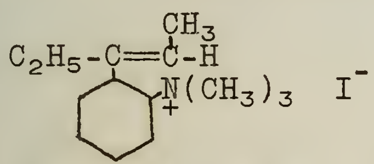
VII

presumable because of the presence of an α-hydrogen atom in the β,β-disubstituted vinyl groups (CH=CRR') employed. With a hydrogen atom in this position the vinyl-benzene link can probably be distorted so as to allow the =CRR' group to pass over the *ortho* substituents.

Restricted rotation was observed in VIII (4), which contains the β,β-dimethyl-α-isopropylvinyl group as the rotating complex, and the cationic group $^+N(CH_3)_3$ as the obstructing *ortho* substituent. It was resolved into stable, optically active components by means of *d*-bromocamphorsulfonic acid, and the *d*- and *l*-iodides obtained showed

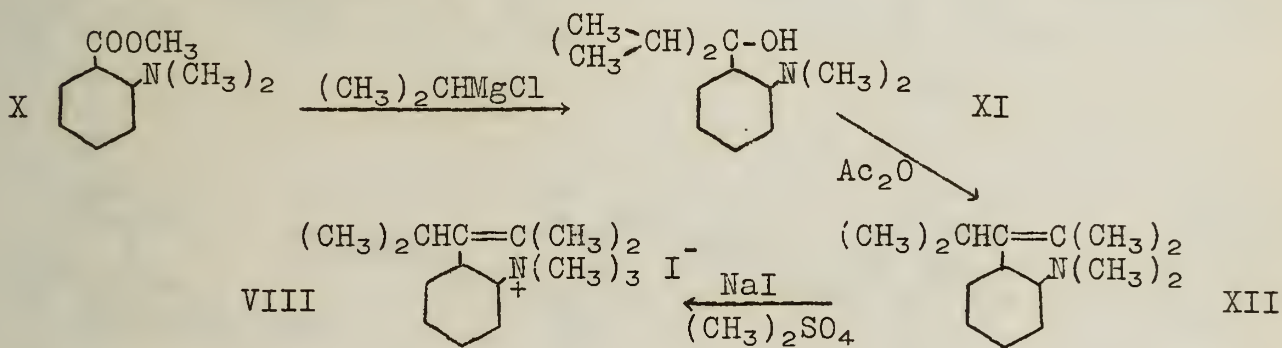
molecular rotations, $[M]_{5461}$, of +55° and -58°. The optically active salts were quite stable; they retained their optical activity after boiling the aqueous solutions for eight hours. This resistance to racemization is in marked contrast to the stability of the compounds containing a substituted amino group as the rotating complex and is in accordance with the large overlap of the groups as indicated by the atomic dimensions concerned.

Compound IX, which differs from VIII in containing the methylethylvinyl group instead of the dimethylisopropylvinyl group as the rotating complex, was found to be non-resolvable, presumably on account of the insufficient overlapping of the substituent groups.



IX

Synthesis of VIII:



X, XI, XII, VIII

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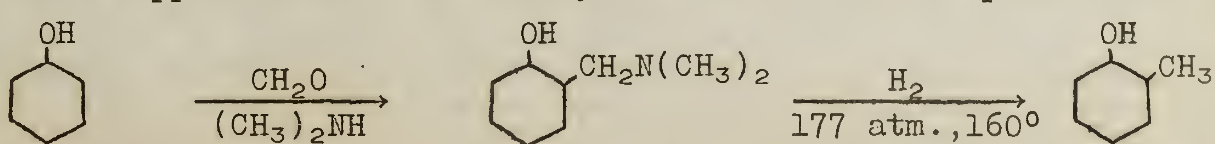
THE NUCLEAR METHYLATION OF PHENOLS

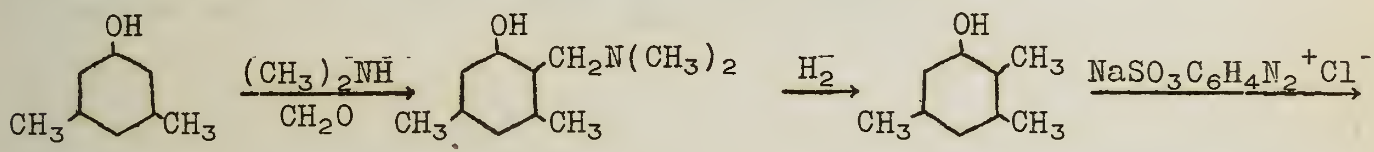
Caldwell -- Temple University

The nuclear methylation of certain phenols is of interest in the preparation of intermediates for the synthesis of certain compounds having physiological action, notably pseudocumohydroquinone which is an intermediate in the synthesis of α-tocopherol. The method involves the preparation of the "Mannich" base by the action of formaldehyde and dimethylamine on the appropriate phenol, followed by hydrogenolysis with copper chromite as catalyst. In the case of phenol itself:

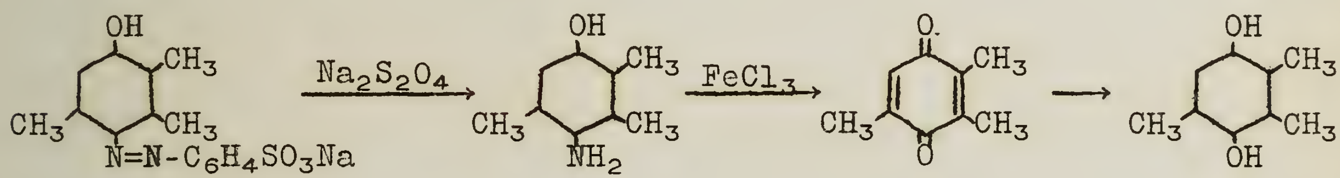


The yield of the Mannich reaction is practically quantitative but is only 30% on the hydrogenolysis. This is explained by the fact that the liberated base poisons the catalyst. If the phenol is acetylated prior to the hydrogenolysis the yield is improved, being 60-70% in some cases. The method is applicable in the methylation of cresols, xylenols, and other phenols and polyhydroxybenzenes, and naphthalenes. The application to aliphatic compounds has not yet been investigated.

Synthesis of pseudocumohydroquinone (VII):- Several syntheses of this compound have been reported in the literature (2,3,4). The method involves the methylation of sym-xylenol (I) to form 2,3,5-trimethylphenol (III). Reduction of a coupling product and oxidation of the amine (V) to the quinone (VI), followed by reduction, gives the desired product:

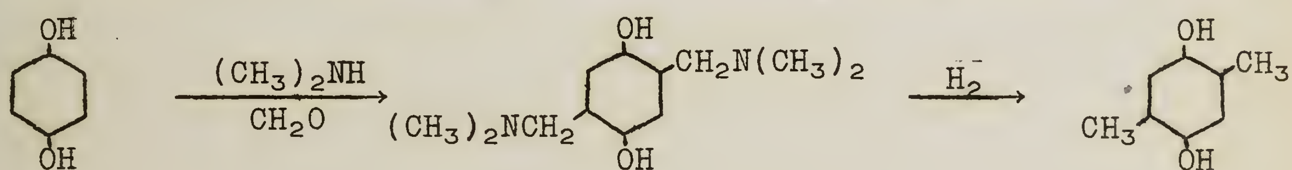


I II III



IV V VI VII

It was thought that pseudocumohydroquinone could be prepared by the direct methylation of hydroquinone, i.e. by treating hydroquinone with three equivalents of formaldehyde and dimethylamine, followed by hydrogenolysis of the Mannich base. Instead, only two methyl groups were intriduced, forming 2,5-dimethylhydroquinone (X).



VIII IX X

Morpholine and piperidine may be used instead of dimethylamine, and the base hydrogenated to the corresponding methyl derivative. For example, the base obtained by treating o-cresol with formalin and morpholine on hydrogenolysis yields vic-xylenol; 3,5,6-trimethylphenol yields 2,3,5,6-tetramethylphenol.

The orientation in all cases is practically completely ortho to the hydroxy group. This is also true in the hydrogenolysis of the bases formed by treating phenols with piperidine and formaldehyde: sym-xylenol yields 2,3,5-trimethylphenol; and α- and β-naphthols yield the β- and α-methyl derivatives respectively. The orientation in the addition of piperidine as reported by Auwers and Domerowski (5), who

stated that the orientation is _para_ whenever this position is open, was shown to be incorrect by hydrogenolysis of the bases and identification of the methyl derivatives so obtained.

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Prepared by F. Richter
May, 1939

THE FORMATION OF QUATERNARY AMMONIUM SALTS FROM DIHALOGENO-PARAFFINS, ETC., IN AQUEOUS ACETONE SOLUTION

Davis, (Miss) Evans, and Hulbert -- Tatem Laboratories, University College, Cardiff

According to Schmidt and Litterschied (1), methylene dibromide and di-iodide react with trimethylamine in alcoholic solution at room temperature thus: $CH_2X_2 + NMe_3 = XCH_2\overset{+}{N}Me_3X^-$; at 100° excess of the amine reacts with methylene di-iodide to give the same product, together with formaldehyde and tetramethylammonium iodide. Trimethyl-β-bromoethylammonium bromide is obtained from ethylene dibromide and aqueous or alcoholic trimethylamine below 50°, but with excess of alcoholic amine at 100°, a variety of products, including the mono- and the di-ammonium salt, is obtained (2). Lucius (3), however, obtained triethyl-β-bromoethylammonium bromide and ethylenebistriethyl-ammonium bromide from the interaction of triethylamine and ethylene dibromide. The mono- and di-ammonium salts were also prepared from the interaction of trimethyl- or triethylamine and trimethylene dibromide. These results suggested that the formation of the di-ammonium salts from methylene and ethylene dihalides is attended with difficulty.

The reactions between a number of organic dihalides and tri-methylamine have now been studied kinetically, in order to find out the extent of the diammonium salt formation and to investigate the factors affecting the formation of quaternary ammonium salts.

The principal results obtained regarding the reactivities of organic halides towards trimethylamine are summarized below, the reaction of only one of the halogen atoms (*) being considered.

$$C_2H_5Cl > ClCH_2\overset{*}{Cl} > ClCH_2CH_2\overset{*}{Cl}$$

$$CH_3Br > BrCH_2\overset{*}{Br} > BrCH_2CH_2\overset{*}{Br}$$

$$BrCH_2CH_2CH_2\overset{*}{Br} > BrCH_2CH_2\overset{*}{Br}$$

$$BrCH_2CH_2\overset{*}{Br} > Br^-(\overset{+}{N}Me_3CH_2CH_2\overset{*}{Br})$$

$$Br^-(\overset{+}{N}Me_3CH_2CH_2CH_2\overset{*}{Br}) > Br^-(\overset{+}{N}Me_3CH_2CH_2\overset{*}{Br})$$

$$BrCH_2CH_2CH_2\overset{*}{Br} = Br^-(\overset{+}{N}Me_3CH_2CH_2CH_2\overset{*}{Br})$$

Two factors (4) affect the velocity of formation of an ammonium salt: (a) anionisation of the halogen atom of the organic halide, facilitated by an electron recession to the halogen; and (b) the co-ordination of the base by means of its unshared electrons to the methylene group of the organic halide, facilitated by an electron recession from the halogen. These are depicted in I. Although the

$$\text{I} \qquad \begin{array}{l} \text{Hal} \\ {\scriptstyle a}\uparrow \\ CH_2 \xleftarrow{\;b\;} :NR_3 \\ \,| \\ R \end{array}$$

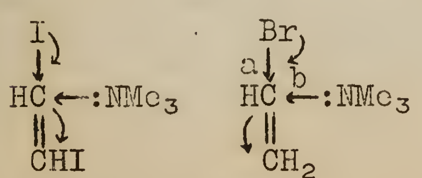
formation of the salt requires the completion of the cycle, it can be considered that the initiation of the cycle depends on either of the factors (a) or (b). Substituents in the organic halide determine the probability of initiation by (a) or (b).

The halogens have complex polar effects, -I, +M. In the methylene dihalides the +M effect, which increases the ease of anionisation of chlorine, may operate, $Cl-CH_2-Cl$, as well as the inductive attractive effect, $Cl-CH_2 \rightarrow Cl$. In the ethylene dihalides, however, the former effect is excluded because of the intercalation of the saturated carbon atom. The greater speed of reaction with trimethylamine of methylene dichloride than of ethylene dichloride (the dibromides are of almost equal reactivity) is, therefore, to be expected.

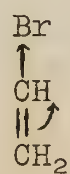
On comparing ethylene and trimethylene dibromides it will be seen that removal of one bromine atom from the other reacting bromine, with a consequent diminution of the attraction (-I) of the one for the other, increases reactivity. Substitution of the strongly attractive group $\overset{+}{N}Me_3$ for Br further decreases reactivity in the ethylene derivatives. It will be noted that, whereas the first halogen in ethylene dibromide is replaced much more readily than the second in the monoammonium salt produced, yet in trimethylene dibromide the diammonium salt is produced as readily as the monoammonium salt. This is due to the greater damping out of the polar effect of the halogen or the $\overset{+}{N}Me_3$ group as it is moved farther away from the reaction center. Electronic effects (-I in these cases) can be transmitted through only two saturated carbon atoms at the most, and it would be expected, therefore, that the attractive electronic effect of $BrCH_2CH_2$- would be less than that of $^{+}NMe_3CH_2CH_2$-, whereas the attractive effects of $BrCH_2CH_2CH_2$- and $^{+}NMe_3CH_2CH_2CH_2$- would be approximately equal.

Consideration of these results indicates that initiation of the electron cycle leading to ammonium salt formation depends on factor (a).

Vinyl bromide and trans-α,β-diiodoethylene are both highly unreactive towards tertiary bases, whereas the related compounds, allyl bromide and 1,4-dibromo-2-butene, are very reactive. Toward dimethylaniline, allyl iodide is more reactive than methyl iodide (5). The vinyl group is considered to have an intrinsic attraction for electrons (-I), as well as a possibility when it is a conjugate system of an electronic displacement, +T (6). The non-activity of the first two compounds, therefore, is due to electron movements (II) retarding anionization of the halogen. Phase III is less important. With allyl bromide (and 1,4-dibromo-2-butene) either of the movements IV or V could take place. In IV there would have to be a change in the mechanism of the initiation of the cycle leading to the formation of the salt, to factor (b).



II



III

$$\overset{\overset{NMe_3}{\downarrow}}{CH_2{=}CH{\leftarrow}CH_2\text{-}Br} \qquad \text{IV} \qquad\qquad \overset{\overset{NMe_3}{|}}{CH_2{=}CH\text{-}CH_2\text{-}Br} \qquad \text{V}$$

The effect of alkyl groups on the speed of the reactions between p-substituted benzyl halides and pyridine (7) and of p-alkyldimethylanilines with methyl iodide (8) where steric effects can be deemed unimportant, is similar to that found with the reaction between alkyl halides and trimethylamine (Me > Et > Pr). Theoretical considerations advanced for the former examples could, therefore, be applied to the simple alkyl halides. An explanation frequently given for this order of the alkyl groups in the reactions of the alkyl halides depends on the steric effects of the groups (9). Although the present work has not decisively shown the absence of steric effects in the reactions being considered, yet it has been demonstrated that the experimental results can be adequately explained by considering the operation of polar effects alone.

Energy of Activation and Probability Factor:- Values of E and log PZ derived from the Arrhenius equation are given in Table I. These values are probably not highly accurate, but they give some useful indications.

Table I

Formation of Monoammonium Salts from Trimethylamine and Dibromides

	E, kg.-cals.	log PZ
(1) CH_2Br_2	16.1	7.3
(2) $BrCH_2CH_2Br$	12.7	5.0
(3) $BrCH_2CH_2CH_2Br$	14.2	6.8

Formation of Diammonium Salts from Bromo-substituted Monoammonium Salts

	E, kg.-cals.	log PZ
(4) $BrCH_2CH_2\overset{+}{N}Me_3\ Br^-$	18.3	8.0
(5) $BrCH_2CH_2CH_2\underset{+}{N}Me_3\ Br^-$	12.5	5.5

Winkler and Hinshelwood (10) showed that, in the reaction of trimethylamine with alkyl halides, the order of increasing E and of decreasing rate of reaction was MeHal, EtHal, Pr^βHal. The increase in E may be attributed to the increasing strength of the C-Hal bond, which might be expected if the initiating factor is a, and the total electronic effect of the alkyl group is in the order Me > Et > Pr^β. On the other hand, the increase in E might be due to steric hindrance, but the results in Table VI do not support this view. The increase in E from (1) or (2) to (4) can be attributed to strengthening of the C-Hal bond in (4) by substitution of $\overset{+}{N}Me_3$ for Br. The greater similarity of the E values for (3) and (5) is to be expected, for now the substituents Br and $\overset{+}{N}Me_3$ have less effect on the strength of the C-Hal bond. Comparing (1) and (2), the fall in E is to be expected from the weakening of the electronic effect of the one halogen on the other in (2). A similar explanation serves for the decrease in E in passing from (4) to (5).

$CH_2=C-N$ … I IV

The effect of alkyl groups on the speed of the reaction between substituted benzyl halides and pyridine (4) and of [illegible] anilines with methyl iodide (5) [illegible] affinity [illegible] is similar to [illegible] [illegible]

[illegible] [illegible] [illegible] given in Table 1. [illegible]

Table 1

[illegible]

(1) [illegible]	15.2	[illegible]
(2) [illegible]	23.7	[illegible]
(3) [illegible]	34.1	[illegible]

[illegible]

(1) [illegible]	[illegible]	[illegible]
(2) [illegible]	[illegible]	[illegible]

[illegible]

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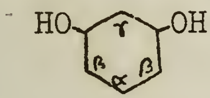
Prepared by R. W. Kell
May, 1939

γ-SUBSTITUTION IN THE RESORCINOL NUCLEUS

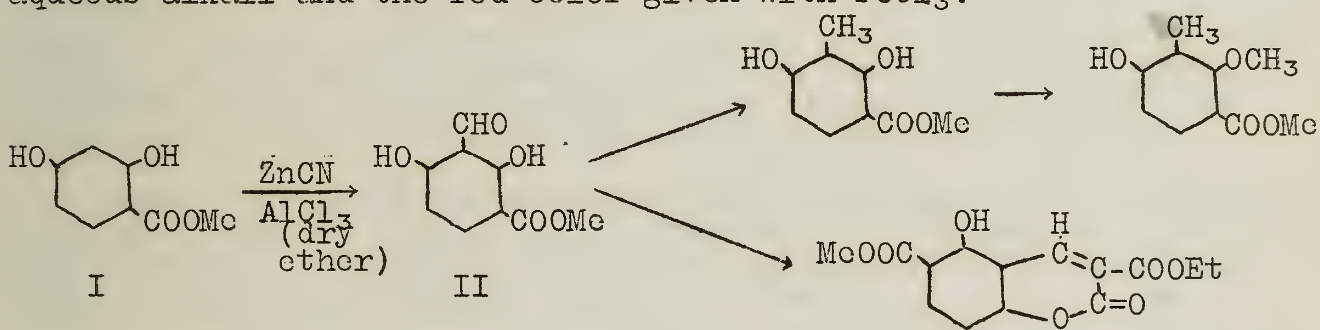
Shah -- Ismail College, Bombay

The Gattermann reaction, when applied to resorcinol or its mono- or dimethyl ethers, gives an almost quantitative yield of 2,4-dihydroxybenzaldehyde. However, when applied to methyl-β-resorcylate by Shah and Laiwalla under the usual conditions, viz., using HCN with aluminum chloride in benzene solution, or with zinc chloride in ether solution, the reaction failed. In the presence of aluminum chloride the reaction proceeded smoothly when dry ether was used as a solvent, and a 63% yield of the γ-substitution product, methyl 2,6-dihydroxy-3-formylbenzoate, was obtained.



The designations used by Shah, referring to the positions on the resorcinol nucleus, are shown.

The product of the above reaction was identified by its reduction (Clemmensen) to methyl 2,6-dihydroxy-m-toluate, which, on partial methylation with sodium methoxide and methyl iodide, gave the known methyl 2-hydroxy-6-methoxy-m-toluate. It gave the characteristic o-hydroxyaldehyde reaction when condensed with ethyl malonate in the presence of piperidine. The product was ethyl 5-hydroxy-6-carbomethoxy-coumarin-3-carboxylate, as indicated by its insolubility in aqueous alkali and the red color given with $FeCl_3$.

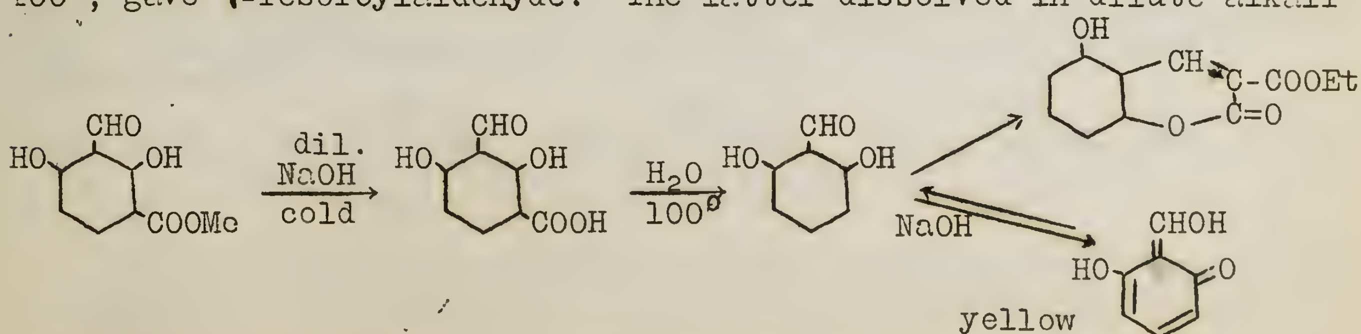


Other reactions of the product II are:

a. With methyl iodide and K_2CO_3 $\longrightarrow$ methyl 2-hydroxy-4-methoxy-3-formylbenzoate.

b. With methyl sulfate and NaOH $\longrightarrow$ methyl 2,4-dimethoxy-3-formylbenzoate. This compound gave the expected product upon reduction with zinc and HCl, which product could also be prepared by methylation of the above methyl 2-hydroxy-6-methoxy-m-toluate.

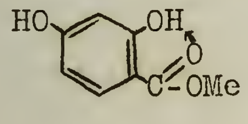
c. Prolonged hydrolysis with cold, dilute alkali gave 2,4-dihydroxy-3-formylbenzoic acid. This, upon heating in water at 100°, gave γ-resorcylaldehyde. The latter dissolved in dilute alkali



with a deep yellow color (probably due to a tautomeric quinoid form), and was reduced to γ-methylresorcinol. A Knoevenagel condensation with ethyl malonate gave ethyl 5-hydroxycoumarin-3-carboxylate.

Similar substitution takes place when β-resacetophenone is formylated by the Gattermann reaction and the structure of the product is indicated by the same general methods. Likewise, if a group is substituted in the 5-position of methyl β-resorcylate, the 3-position is formylated.

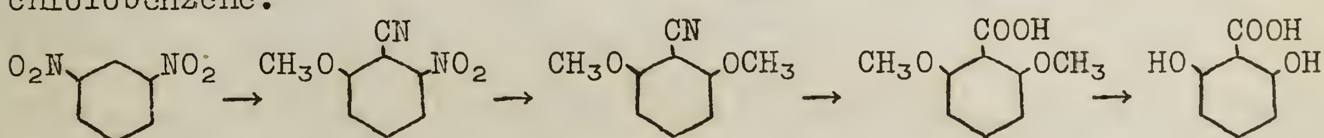
The explanation for the predominance of γ-substitution - this being the first example of the particular type discussed above - is given by Shah as being due to a fixation of bonds in the Kekule formula by chelation between the carbomethoxy and the o-hydroxy groups in methyl β-resorcylate, requiring the presence of a double bond between the carbon atoms bearing these two groups.



Very few instances of direct substitution in the γ-position have been recorded and there always seems to be a greater quantity of β-substitution. Baker and Carruthers have shown that, in β-substituted resorcinols, the position taken by the incoming group depends upon the group already substituted in the ring, and, in all cases observed up to that time, the predominating reaction was to give the symmetrically substituted ring. This led to the idea that there was no fixation of the bonds in the ring as a result of chelation, and the normal directing influences of the groups are free to manifest themselves. Mills and Nixon have pointed out that, when such phenolic compounds react, the substitution takes place on the carbon atom attached by a double bond to the carbon carrying the hydroxyl.

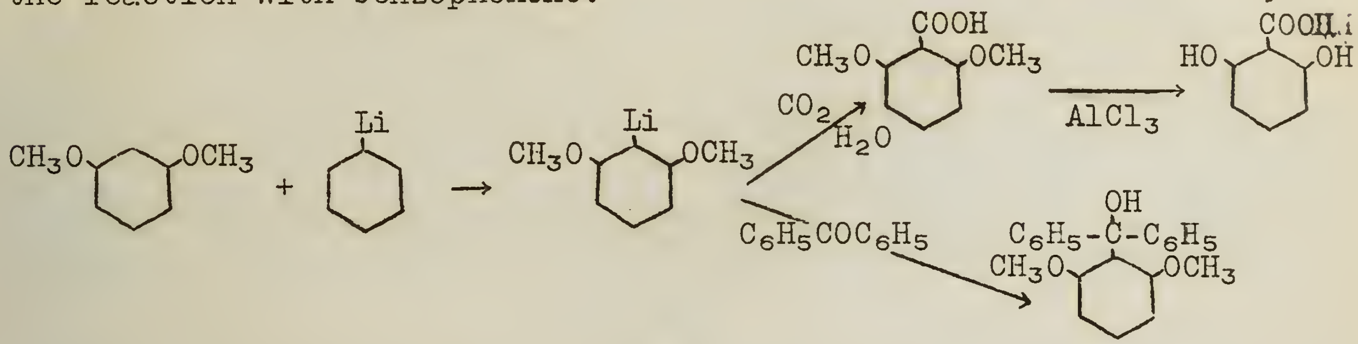
Other methods of substituting in the γ-position of resorcinol have been advanced. Shah calls attention to a "highly involved" synthesis reported by Limaye in which he demethylates 2,6-dimethoxybenzaldehyde using aluminum chloride in benzene.

A few of the older syntheses for the introduction of a carboxyl group into the γ-position involved such methods as heating resorcinol with ammonium carbonate in a sealed tube, and heating with potassium bicarbonate in glycerol. The yields were all low, most of the substitution being directed to the β-position. Later, Mauthner, working on the basis of an observation of Lobry de Bruyn, heated m-dinitrobenzene with potassium cyanide in methyl alcohol. The resulting compound contained a nitro-, a methoxyl- and a cyano-group in the proper relationship to afford a method of synthesis of carboxyresorcinol. By heating this substance with methyl alcohol and KOH, he obtained the 2,6-dimethoxybenzonitrile, which on hydrolysis, gave the corresponding acid. The methyl groups were then removed with aluminum chloride in chlorobenzene.

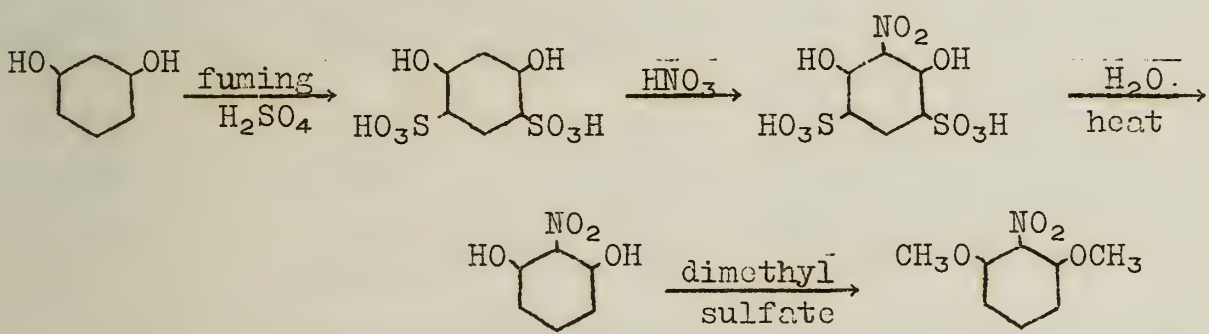


Wittig and Pockels have very recently employed phenyl lithium as a reagent for substituting in the γ-position of resorcinol methyl

ethers. Lithium goes into the ring and the product may be used for synthesis of other compounds. These investigators mention the preparation of the corresponding acid, using CO_2, and of a tritanol from the reaction with benzophenone.



The preparation of γ-substituted resorcinols is best accomplished by an indirect method. Though nitration of resorcinol is unsuccessful, by first sulfonating to obtain the disulfonic acid derivative (symmetrical) and then nitrating, a product is obtained, which, on hydrolysis, results in the 2-nitroresorcinol.



Kauffmann has prepared the dimethyl ether of the nitro-compound and has converted this to a number of other derivatives. For example, he reduced the nitro group, diazotized the resulting amine and replaced the diazonium group with Br, I, and CN. It is worthy of mention that all of these reactions are greatly influenced by steric effects which do not seem to act when the free hydroxyl groups are present.

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Prepared by J. W. Shackleton
May, 1939

Kohlrausch, K.W.F.

Origin of Raman Spectra:- Raman spectra owe their origin to the interaction of a light quantum hv and a molecule. In this effect each mode of oscillation in the molecule which interacts with the light quantum results in the absorption of energy from this quantum and its consequent rescattering with less than its initial energy. Since each type of vibration or rotation gives rise to a Raman line, in a diatomic molecule only one line is probable. These vibrations are analogous to a simple mechanical system consisting of two masses held together with a spring. The frequency with which they vibrate is represented by

$$v = \frac{1}{2\pi}\sqrt{F/\mu}$$

where F is the force per unit displacement, μ is the reduced mass, and v is the frequency in wave numbers per centimeter. v is found on the photographic plate as the shift in frequency of the scattered light with reference to the incident light.

A system of 3 atoms of the type AX_2 may exist in a linear or non-linear form. The modes of vibration of the non-linear form is illustrated in Fig. 1. Here the asymmetric oscillation is indicated by (A), the symmetric by (B) and the deformation motion by (C). For the linear model the shifts may be calculated and are in reasonable accord with the experimental observations.

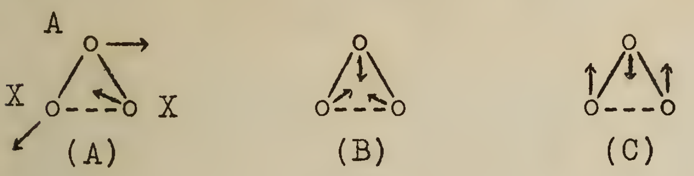

Fig. 1

It has already been indicated that the magnitude of Raman shifts are a function of the force exerted between the atoms, the type of motion, and the relative masses of atoms. As the masses decrease the Raman shifts increase. Therefore the shifts corresponding to the linear or symmetric oscillation of the C-H bond are of large magnitude. They vary from 2800 cm^{-1} to 3400 cm^{-1}, the rather wide deviations being due to variations in the force constant with constitution. Between 1100 and 1460 cm^{-1} lie the deformation oscillations of the C-H bond. The C-C linkages present a very complex problem. The lines which lie between 800 and 1100 cm^{-1} are generally attributed to this linkage. The total number of lines which occur will depend on the molecular configuration and the interaction of valence forces.

Charateristic Frequency:- The characteristic frequency is the frequency obtained from the oscillation of a C-X bond, which is the linkage of the carbon chain and a substituent. It is designated as w_1. The symbol w_0 is used to designate Eigenfrequencies which refer to the oscillations of an isolated bond. In table I are listed w_1 values for some tertiary-butyl derivatives.

Table I

$(CH_3)_3C$-	-H	-OH	$-CH_3$	-SH	-Cl	-Br	-I	——
w_1	796	746	730	587	570	515	484	436

If the substituent X is heavy compared to CH_3 and the C-X (w_0) value is small compared to the C-C (w_0) frequency, we have the case where most of the shifts become independent of X. The exception is the w_1 frequency. If one considers the mass of X becoming infinitely heavy, then the force between the C and X grows infinitely small; finally the case is reached where the $(CH_3)_3C$- is bound to an unyielding wall by an infinitely weak spring. In this manner we may obtain some information as to the vibrations of the radical by itself.

The situation is similar if the w_0 value for the substituents is appreciably higher than that of the C-C bond, as is the case with ≡C-H, -OH, -NH, -SH, -C=O, -C≡N. For these more complex substituents several valence frequencies are found. In the divalent carbonyl and the tetravalent ethylene groups the situation is remarkably complex. The carbonyl frequency depends only slightly on the branching of the attached carbon chains. It varies considerably in the different functional groups which contain it. The shift lies approximately at 1654 cm^{-1} for acids, 1710 cm^{-1} for methyl ketones, 1720 for aldehydes, 1735 for esters, and at 1795 for acid chlorides. Following is a list of some shifts attributed to variously substituted ethylenes.

$H_2C=CH_2$ 1623 cm^{-1}	$RHC=CH_2$	1647 cm^{-1}	$RHC=CHR'$	1658 cm^{-1}	(trans)
	$R_2C=CR'_2$	1678 cm^{-1}	$RHC=CHR'$	1674 cm^{-1}	(cis)

The Raman spectra for C=C linkages fall into the region 1600-1700 and are more or less completely separated from any lines due to any other type of oscillation. These lines are sharp and can be measured with accuracy. Therefore the effects of mass and of binding force can be determined with considerable exactness. This opens up a more or less endless avenue in the investigation of constitutional problems where ethylenic linkages are involved. It may be stated categorically that any straight chain and most cyclic compounds having the structure -Ċ=Ċ- show a Raman shift in the 1600 region. If the structure is -Ċ=C=Ċ- this is not true. If the structure is a conjugated one, the characteristic 1600 line is lowered by about 20 cm^{-1} and its intensity is increased.

Cis-Trans Isomerism:- It has been found that with reference to the C=C oscillation, the trans compound has a shift greater by 15 cm^{-1} than the cis compound. It is quite possible to determine the composition of mixtures containing cis and trans forms, and to follow the change in composition on distillation by its spectra.

Free Rotation:- 1. In going from 1,1-dichloroethane to 1,2-dichloroethane the number of lines between 0-1600 increases from approximately 11 to 17 although the number of chain members is the same. This seems to indicate an increase in the number of molecular forms.

2. The sharpness and the brightness of the lines has not changed. It should be remembered that in the cis and trans forms of 1,2-dichloroethylene two distinct and separate Raman spectra were found. If we are to assume all possible configurations for 1,2-dichloroethane, we should have bands for the Raman spectra instead of lines.

3. In going from 1,2-dichloroethane to 1,2-dibromoethane, the number of lines again increases.

4. There are depolarized frequency lines. These are only possible in the spectra of a four-membered, open chain if both cis and trans forms are present.

Conclusions: There are definitely semi-stable cis and trans forms present in 1,2-dichloroethane. The presence of intermediate forms are not necessary to explain the spectra obtained. Since no band spectra is obtained, their presence is unlikely. The relative amounts of the cis and trans forms can be calculated from intensity and polarization measurements. In the solid state, 1,2-dichloroethane exists only in the trans form.

Tautomerism:- The demonstration of keto-enol tautomerism was one of the earliest applications of the Raman effect. The classical work was done on the acetoacetates. More recently ketimid-enamine isomerism has been investigated in this manner.

Ring Strain:- Below are given some frequency values for some linkages in saturated cyclic compounds.

Y = radical	w (C-C)	w(C-H)	w (C=O) in YCOR
C_2H_3	1640	3080	1718
C_3H_5	1188	3011	1719
C_4H_7	950	2920	1722
C_5H_9	890	2873	1724
C_6H_{11}	800	2854	—
C_7H_{13}	729	2858	—
C_8H_{15}	700	2857	—

When we remember that the frequency is proportional to the square root of the binding force, we see that with increase in ring members the C-C and C-H binding forces decrease whereas the C=O binding force in the external shain increases.

Disubstituted Benzenes:- The fact that para derivatives have less lines for a given range than the corresponding ortho and meta derivatives indicates that the para derivatives have a greater symmetry.

In closing it might be well to remark that the number of lines found are large and increase with the complexity of the compound. Thu it is evident why only relatively simple molecules have been studied.

The magnitude of the shifts is not the only consideration involved in matching and following the changes in frequency with the changes in the compounds. Two other parameters which may be invoked are the intensities and the degree of polarization. In Raman spectra the symmetrical oscillations are the most intense and most strongly polarized.

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May, 1939